Drug Class Review
on
Macrolides

Final Report
Evidence Tables

August 2006

The Agency for Healthcare Research and Quality has not yet seen or approved this report

The purpose of this report is to make available information regarding the comparative effectiveness and safety profiles of different drugs within pharmaceutical classes. Reports are not usage guidelines, nor should they be read as an endorsement of, or recommendation for, any particular drug, use or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

George P. Allen, PharmD
David T. Bearden, PharmD
Michelle D. Liedtke, PharmD
Theresa M. Bianco, Pharm D
Tracy L. Dana, MLS

Oregon Evidence-based Practice Center
Oregon Health & Science University
Mark Helfand, MD, MPH, Director

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Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Anderson G 1991 United Kingdom	dbl blind, randomized; 57 practictioners sites	>=18 years, s/s followed up with a CXR	clari 250mg po BID vs erythromycin stearate 500mg QID for 14 days	Day 14, and 6-8 weeks Evaluable if: took 70% of study drug OR at least 12 doses and had f/u CXR cure: undefined success: cure + improvement	Day 14, 6-8 weeks microbiology and serology	92 F/ 116 M 206 white, 2 asian 53.5 Y (18-89)
Block, 1995 USA	single blind (invest), R, multicenter	children 3-12 CAP confirmed w/X-ray	clari 15mg/kg/d divided q12 * 10d vs EES 40/mg/kg/d divided BID or TID * 10d	1-2d post tx, 4-6 wk f/u cure: resolution s/s improvemnet: improved but not resolved success: cure or improvement failure: no change or worsened recurrance: cure with relapse by week 6	1-2d post tx, 4-6 wk f/u eradication: absence of organism or clinical cure without sputum to test	90 pts 3-4 years old, 98 5-7 yrs, 72 8-12 years clari 81 male/52 female; ery 59 males/68 female (more males in clari group) p0.025 161 white 67 black 3 asian 29 Other

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Anderson G 1991 United Kingdom	stated no difference severity of illness (though defintion not reported)	NR/NR/208	100/1/108 (66 excluded b/c did not confrim pneumonia - CXR?) 4 clari and 11 ery premature discontinuation	Evaluable pts only 2 weeks: clari vs ery cure: 52% vs 40%, p=.242 success: 98% vs 91%, p=.155 6-8 weeks clari vs ery cure: 77% vs 80%, p=.810	clari vs ery only reported for evaluable patients eradication: 8/9 vs 5/5	COSTART dictionary
Block, 1995 USA	mild (transient and easily tolerated), moderate (discomforting and disruptive of daily activity, severe(incapacitating, life-threatening, or considerably interfering with daily activities) 15-22% mild, 78-80% moderate (for C.pneumoniae and M. pneumoniae)	NR/NR/ 260 enrolled	NR/NR/234 evaluable (explained where all patients excluded come from).	clari vs ery cure: 84 vs 76%, p=.1871 success: 98 vs 95%, p=.480 failure: 2 vs 5% recurrance 1/121 (0.8%) vs. 5/105 (5%)	clari vs eri 24/27 (89) vs 16/18 (89) NR	patient report

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Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Anderson G 1991 United Kingdom	mean duration of therapy: 13 days clari vs 10 days ery All AE: clari vs ery GI 7% vs 27%, p=0.001 overall 19% vs 35%, p=0.004	4 calri, 21 ery w/d due to SE	39/208 patients w/ + cx: H.flu (62%), pneumococcus (18%) 16pts w positive serology The ITT analysis includes many patients who did not have radiologic evidence of pneumonia (so, no
Block, 1995 USA	overall 24% (32pts) clari, 23% ery (29pts) - no numbers but, "mostly GI and mild to moderate"	clari 3, ery 5	122 patients with culture or serology, 74 c.pnumoniae, 69 m.pneumoniae (mostly atypicals identified) 47% with pathogen identified

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Bradbury 1993 Ireland, germany	randomized, open-label, multicenter	AIECB diagnosed on clinical history, physical findings, and where possible organism isolation. Pneumonia included Chest X-ray	azi 500mg x 3day vs clari 250mg po BID for 10d	10-14d after end of therapy cure: alll s/s disappeared improved: partical disappearance or improvement filed: no change or worsening relapsed: initial improvement followed by worsening	blood and sputum cx, d 10-14 eradicated: not isolated on f/u or no sputum to test colonization: organisms not considered pathogens isolated eradication/re-infection: baseline pathogen eradicated then reappeared superinfection: no pathogen isolated requiring treatment	entire study azi vs clai 148M/104F vs 152M/106F 52.2 (18.1-84.4) vs 53.9 (18.2-91.7) NR by diagnosis #'s azi vs clari acute bronchitis 172 vs 186 (not included in further anlysis here) AIECB 75 vs 68 pneumonia 5 vs 4

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure	Microbiological Cure	Method of adverse effects assessment
Bradbury 1993 Ireland, germany	no difference in disease severity or frequency or smoking in groups for AIECB no difference pneumonia	NR/NR/510(entire study) 143 enrolled AIECB 9 enrolled pneumonia	22/NR/488 (entire study) 138 evaluated AIECB 8 evaluable pnuemonia	d10-14 azi vs clari AIECB cure: 68 vs 64% improved: 27 vs 33% failed: 5 vs 3% pneumonia (n=8) cure: 50% vs 50% improved: 25 vs 50% failed: 25 vs 0%	day 10-14 azi vs clari AIECB eradicated:25/25 vs 27/29 pneumonia eradicated: 1/1 vs 0/0	patient reports

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Bradbury 1993 Ireland, germany	AE (whole study) azi vs clari 22/252 (9%) vs 16/258(6%) GI: 15/252 vs 10/259 abd pain: 1/252 vs 3/258 diarrhea: 9/252 vs 2/258 nausea: 1/252 vs 1/258	1 azi and 3 clari w/d due to SE	needed to take 50% meds to be eligible for analysis, only 1 pt excluded for this

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Chien, 1993 Canada, Sweden	randomized, double-blind multicenter	>12 years, radiographic new infiltrate, positive culture or subsequent culture or serologic findings	clari 250 q12 * 7-14d vs. erythro stearate 500 q6 * 7-14d	48h post last dose and 4-6 wk f/u cure: resolution all s/s improvement: partial resolution faulre: no improvement relapse: deterioration after initial improvement	48h post last dose and 4-6 weeks post cure: absence of pathogen failure: persistance of pathogen reinfection: new organism recurrance: reappearance of previously eradicated organism	47.2y (12-93)clari, 48.2y ery (18-90) NS 88M, 85 F 171 white, 1 black , 1 asian

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**	**Clinical Cure**	**Microbiological Cure**	**Method of adverse effects assessment**
Chien, 1993 Canada, Sweden	NS differences in severity mild and moderate infection % (defintions not defined) clari vs ery mild: 32 vs 27pts moderate: 60 vs 54pts	NR/NR/268 enrolled	95 withdrawn/NR/ 173 evaluated well tolerated for who was excluded, all equal in each group	specfic timeframe not indicated clari vs ery cure: 57/92 vs 43/81 improvement: 32/92 vs 35/81 failure: 3/92 vs 3/81, NS	Timing not indicated 23/26 clari 17/17 ery p=.287 16 clari pts, 11 ery had serology positive for M.pneumoniae or C.pneumoniae	undefined at each follow-up visit

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Chien, 1993 Canada, Sweden	total adverse events 41/133 clari vs 79/135 ery, p<0.001 GI 25/133 clari, 70/135 ery, P <0.001	clari 6/133. ery 37/135, p<0.001	

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Daniel 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	multicenter, randomized, non-blinded (except to culture results, which were blinded)	>18 years old, acute bacterial infection including acute infectiouus exacerbations of chronic bronchitis and pneumonia(no further definitions of infection added) CXR not required or mentioned	azi 500mg x 1day then 250mg QD on days 2-5 vs erythromycin stearate 500mg QID for 7-10d. (7 day target with option to extend to 10d if deemed "appropriate")	d10-15 comparison of pre-treatment s/s changes	d10-15 eradication: organism not cultured again, or lack of sputum production	93M/88F (entire study) 84/88 white
Harris, 1998 USA	multicenter 23 sites 2:1 randomized dbl blind	5 - 16y radiographic evidence Note: age determined comparitors 6mos to 5 yrs amox/clav, 5-16 erythro, only ery group included here	azi 10mg/kg *1d, then 5mg/kg days 2-5 vs erythromycin estolate 40mg/kg/d in 3 divided doses for 10 days (or amox/clav if <5 yrs; data not included)	Day 15-19 and 4-6 weeks post tx cure: complete resolution S&S Improvement: incomplete resolution s&s failure: persistence or worsening of S & S	Day 15-19 micro and serology eradication: if - cx or clinical resolution after initial positive persistance: failure to eradicate or no cx done, but clinical failure and switched therapy	53.7% M/46.3%F azi; comparitors (both) 61.5%M,38.5% F 5.53y(0.5-15) azi; 5.22 (0.5-15) comparitors black 22.8% azi, 20% comp white 72.6% azi, 74.8% compar other 4.6% azi, 5.2% comp (ery group demographics not seperated from 2 comparitors)

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**	**Clinical Cure**	**Microbiological Cure**	**Method of adverse effects assessment**
Daniel 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	all bronchitis 77% azi, 75% ery (AECB not split in %, though) Pneumonia 23% vs 24% of total population in study	NR/NR/181 (total study) 42 pneumonia 138 all bronchitis (# AECB not individually stated)	NA/NA/NR	azi vs ery pneumonia 86 vs 74% AECB 64 vs 47% NS, N not reported for AECB	azi vs ery eradicated 80 vs 86% (For entire study, incluing bronchitis of all types)	Voluntary patient reporting
Harris, 1998 USA	no differences in baseline S &S	NR/NR/456	36/0/420	azi vs ery day 15-19 cure: 75.7% (115pt) vs 77.6% (52pts) improvement: 21.7% vs 20.9% failure: 2.6% vs 1.5% week 4-6 cure: 95.1% vs 88.7% failure: 4.9% vs 11.3%, NR/NS	azi vs ery c.pneumonia eradication: 9/12 vs 6/6 mycoplasma eradication: 11/11 vs 4/6	patient report

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Daniel 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	whole study azi ve ery all AE: 5% (5/93)vs 18%(16/88)	1 ery w/d due to AE	poor study, incomplete diagnostics, and no spilt in # of patients in each area
Harris, 1998 USA	azi (n=163) vs ery (n=75) total AE: 17(10.4%) vs 15 (20.0) diarrhea: 10/163(6.1%) vs 17/75 (22.7%) vomitting: 15 (9.2%) vs 22 (39.3%) abd pain: 12 *(7.4) vs 15 (20.0) nausea: 9(5.5) vs 8(10.7)	azi vs ery d/c due to AE 3 (1.8%) vs 1 (1.3%)	80% drug taken for clinically evaluable in whole study more treatment failures (regardless of group) in patients >5 yrs old (8% vs 2%); the >5 much more liekly (2-3x)to be serologically positive for atypicals 62 to 66% c.pneumoniae 41-43% M.pneumoniae 2% others

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Jang, 1995 Taiwan	single center, randomized, blinding not mentioned	no age limits, CXR required	clari 250mg po BID vs erythromycin (not specified salt) 500mg QID for 14 days	timing not included Evaluable if CXR positivie and received 3 days drug time of f/u not included cure: resolution of symptoms improvement: alleviation of symptoms without cure failure: lack of favorable response or deterioration	Not done	14F/25M clari 53.6(20-81);ery 54.3 (16-76) race NR
Kogan, 2003 Chile	single center, randomized, blinding not mentioned	1 month - 14 y radiologic diagnosis split into: atypical vs typical presentation (azi vs ery for atypical presentation reported here; also did azi vs amox for typical , NR here) entry to atypical group, via 2 investigators ruling: prominent cough, variable fever, few signs of consolidatio, CXR: mixed alveolar-interstitial pattern (~1/2 of presented cases)	azi 10mg/kg *3d vs ery 50mg/kg/d in 3 divided doses for 14d (or amox 75mg/kg/d divided 3x/d for 7d not reported)	Day 14 cure: resolution of fever, cough/wheezing/rales	micro, serology, PCR	azi 62.6 mos vs 56.2mos gender ratio M/F 1.2 ery ethnicity NR

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Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure	Microbiological Cure	Method of adverse effects assessment
Jang, 1995 Taiwan	no severity differences reported	NR/NR/40	0/0/20	timing not included clari vs ery cure: 65% vs 65% improvement: 30% vs 25% cure or improve: 95% vs 90% failure: 5 vs 10%	NR	method not stated
Kogan, 2003 Chile	no differences baseline S&S	NR/NR/59	0/0/59	azi vs ery 3.6% with sx vs 7.7% w/sx (weezing only, no fever or rales/crackles for any)	NR	method NR

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Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Jang, 1995 Taiwan	GI side effects clari vs eri: 1/20 vs 6/20	2 ery w/d due to SE, 0 clari	12 pts 30% w/organisms: 3pneumococcus, 8 atypicals
Kogan, 2003 Chile	azi 0/33 SE vs 3/26 ery all 3 diarrhea	0 d/c	split into typical vs atypical suspect…. ~1/3 each group w/ atypicals pts <3mos were hospitalized by Chilean convention 3 in azi group vs 7 in ery group, p=0.09

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Muller 1993 Germany and Ireland	multicenter, randomized, blinding not reported	>12 years, otitis media;sinusitis; pharyngitis or tonsillitis clinical history, physical findings for pharyngitis: +cx S.pyogenes	Azithromycin 500mg QD * 3d vs. clarithromycin 250mg BID for 10d	d10-14 cure: disppearnce of clinical s/s improvement: improvement in or partial disappearance of s/s failure: no change or worsening s/s relapse: improvement or cure followed by worsening also d21-18 for strept pharyngitis	d10-14 eradication: eradication or no culturable material (absence of cough) superinfection: new pathogen that requires treatment persistence: persistance of all pathogens recurrance or reinfection not evauable: no organism isolated also d21-28 for strept pharyngitis	azi vs clari 117M/74F vs 109M/80F 40.6 (12.4-82.0) vs 38.8 (12.9-79.4)yrs ethnicity NR

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**	**Clinical Cure**	**Microbiological Cure**	**Method of adverse effects assessment**
Muller 1993 Germany and Ireland	# pts/indication azi vs clari otitis: 34 pt vs 36 sinusitis: 75 vs 74pts pharyngitis/tonsillitis: 82 vs 79pts	NR/NR/380	23/11/357	azi vs clari Otitis media cure: 26(79%) vs 26 (74%) improved: 18% vs 23% failed: 3 vs 3% sinusitis cured: 49(66%) vs 48(68%) improved: 27 vs 27% failed: 7 vs 6% pharyngitis/tonsillitis cure:54(76%) vs 54(74%) improved: 20 vs 23% failed: 3 vs 1% relapsed: 1 vs 1% NS for any	d10-14 azi vs clari Overall repsonse: 94% vs 95% Otitis media eradicated: 3/3 vs 6/6 Sinusitis eradicated: 35/38 vs 27/29 Pharyngitis/tonsillitis: 37/39 vs 37/39 day 21-28 33/36 vs 33/36	volunteered by patient

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Muller 1993 Germany and Ireland	azi vs clari overall: 16/191 (8%) vs 14/189pts (7.4%) abd pain: 5 vs 0pts diarrhea: 5 vs 2pt dyspepsia:0 vs 1pt gastritis: 0 vs 2pt hiccups: 0 vs 1 nausea: 2 vs 3 vomiting: 1 vs 1pt	3 azi (2 abd pain, 1 vomiting) 3 clari (nausea, prurits, MI[causality unknown])	

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
O'Doherty 1998 Ireland, Germany, 2 others not specified	28 centers, 4 countries; not blinded	12-75 years old New infiltrate and s/s, excluded if gram stain revealed gram negative rod unlikely to be covered (e.g., Enterobacteriacea, psudomonas, klebsiella) - note H.flu should be distinguishable on gram stain	azithromycin 500mg po QD * 3d vs clarithromycin 250mg BID for 10 days	day 12-16 (if improved only at day 12-16 second f/u on day 19-23) cure: disappearance of all s/s improvement: partical disappearance or improvement of s/s failure: no change or worsening relapse: improvement with subsequent worsening	day 12-16 and 19-23 micro and serology eradication: elimination of pathogens OR absence of culturable material (sputum) persistance: presence of organism at conclusion of study recurrance: reappearance of organism after initial clearing re-infection: eradication of baseline pathogen followed by new pathogen requiring treatment	50.1 (14.1-75.2) azi, 51.5 (12.5-78.9) clari; azi 60M/41F, clari 59M/43F)

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure	Microbiological Cure	Method of adverse effects assessment
O'Doherty 1998 Ireland, Germany, 2 others not specified	NR	NR/NR/203	27/NR/176	Day 12-16 azi vs calri cure: 65% vs 69% improvement: 30% vs 26% failure: 6% vs 5% NS cure/improvement rates p=0.518 for 49 pts improved at day 12-16, f/u on day 19-23: azi vs clari cure:79% vs 68% improvement: 17% vs 27% failure: 4% vs 5% NS cure/improvement rate p=.486	azi vs clari eradication 31/32 (97%) vs 32/35 clari (91%) all 7 serologic positive patients cured	patient report or investigator observation

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
O'Doherty 1998 Ireland, Germany, 2 others not specified	AE related to treatment in 203 pts (per investigators): 14 (14%) azi, 13 (13%) clari, p=.815 7 azi, 8 clari w/ GI events	4 clari, 1 azi discontinmued/2 clari pts due to adverse effects, 0 azi	lose dose clari for adult CAP, H. influenzae most common (18 azi, 16 clari), S.pneumo 2nd (6 azi, 16 clari).

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Sopena, 2004 Spain	5 centers, open label, randomised	Adults >18, mild to moderate CAP (not defined), needed CXR new infiltrate	azithromycin 500mg po QD * 3d vs clarithromycin 250mg BID for 10-14 days	day 10-13 day 25-30 cure, improvement, failure (no definitions given) per protocol: 3-4 visits and 80% of drug taken ITT: all with 2 or more visits	Not done	41.7 mean age (azi); 44.4 clari gender NR race NR

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure	Microbiological Cure	Method of adverse effects assessment
Sopena, 2004 Spain	NR	NR/NR/70	7/nr/63 (per protocol group)	Per protocol: azi vs. clari day 10-13 cure: 58.1 vs 68.8% improve: 38.7% vs 25% not evaluable: 0 vs 6.2% day 25-30 cure: 90.3% vs 87.5% improvement: 6.5% vs 3.1% failure: 0 vs 0 not evaluable: 0 azi 1 pt clari ITT not specified, stated no differences	NR	method not reported

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Sopena, 2004 Spain	overall AE: 26.5% azi, 25% clari non-compliance (not defined): azi 0 pts, clari 15 pts	NR	low dose of clari for adult CAP; 22.8% etilogy known - 4/16 pneumococcus, 6/16 m.pneumoniae, 4/16 Legionella(! high #)

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Study Design Setting**	**Eligibility criteria**	**Interventions**	**Method of Outcome Assessment and Timing of Assessment**	**Method of Microbiological Outcome Assessment and Timing of Assessment**	**Age Gender Ethnicity**
Wubbell, 1999 USA	single center, randomized, unblinded	5 - 16 yrs radiographic evidence	azi 10mg/kg *1d, then 5mg/kg days 2-5 vs erythromycin estolate 40mg/kg/d in 3 divided doses for 10 days (or amox/clav if <5 yrs; data not included)	10-37d post therapy cure: resolution s/s failure: persistance or progression or new infection	micro, serology	174 pts: (47% 0-2; 16% 3-4) 25% 5 to 8, 12% 9-16 only >5 included in analysis here 92 AA, 54 latin, 23 casusaian, 2 "oriental", 2 Indian, 1 Pakastani

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure	Microbiological Cure	Method of adverse effects assessment
Wubbell, 1999 USA	No differences	NR/NR/174 (168 screened for etiology)	total group 21/10/147 azi vs ery group NR/NR/59	azi vs ery cure: 30/30 vs 28/29 (ascertained numbers from text descriptions)	NR for groups	method NR

Evidence table 1. Summary of community-acquired pneumonia (CAP) trials

Author, Year Country Trial Name (Quality Score)	**Adverse Effects Reported**	**Total withdrawals; withdrawals due to adverse events**	**Comments**
Wubbell, 1999 USA	azi vs ery (includes all azi pts regardless of age) total AE likely drug related: 10/69 (14%) vs 8/29 (25%) diarrhea: 3/69 vs 2/29 abd pain: 2/69 vs 0/29 vomiting: 1/69 vs 1/29 nausea: 0/69 vs 1/29	11 withdrawals total study, # due to AE unclear	excluded if drug interactions likely not evaluable if <80% drug taken total group 47% etology identified: 20% viral, 27% pneumococcal

Evidence table 2. Quality assessment of CAP trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/ high	Intention-to-treat (ITT) analysis	Post-randomization exclusions
	Internal Validity										
Anderson 1991	NR	NR	y	y	y	y	y	y,NR,NR,NR	n	y	y
Block 1995	NR	NR	y	y	y	y	n	y,NR,NR,NR	n	n	y
Bradbury 1993	NR	NR	y	y	n	n	n	n,n,n,n	n	n	y
Chien 1993	y	NR	y	y	y	y	y	y,n,y,n	n	n	y
Daniel 1991	NR	NR	y	n	n	n	n	n,n,n,n	n	n	y
Harris 1998	NR	NR	y	y	y	y	y	y,NR,NR,NR	n	n	y
Jang 1995	NR	NR	y	y	NR	NR	NR	y,NR,NR,NR	n	y	n
Kogan 2003	NR	NR	y	y	NR	NR	NR	y,NR,NR,NR	n	n	n
Muller 1993	y	NR	y	y	n	n	n	y,n,n,n	n	n	y
O'Doherty 1998	NR	NR	y	y	n	n	n	y,NR,NR,NR	n	n	y
Sopena 2004	NR	NR	y	y	n	n	n	y,NR,NR,NR	n	y	n
Wubbel 1999	NR	NR	y	y	n	n	n	y,NR,NR,NR	n	n	y

Evidence table 2. Quality assessment of CAP trials

Author, Year Country	**Quality Rating**
Anderson 1991	fair
Block 1995	fair
Bradbury 1993	fair
Chien 1993	good
Daniel 1991	poor
Harris 1998	fair/good
Jang 1995	fair
Kogan 2003	fair
Muller 1993	fair
O'Doherty 1998	fair
Sopena 2004	fair
Wubbel 1999	fair

Evidence table 2. Quality assessment of CAP trials

Author, Year Country	**Number screened/eligible/eNRolled**	**Exclusion criteria**	**Run-in/Washout**	**Class naïve patients only**	**Control group standard of care**	**Funding**	**Relevance**
	External Validity						
Anderson 1991						NR, 3/5Abbott authors	
Block 1995				NR		Abbott Laboratories	
Bradbury 1993						NR	
Chien 1993				NR		Abbott Laboratories	
Daniel 1991						Pfizer	
Harris 1998				NR		Pfizer	
Jang 1995				NR		NR	
Kogan 2003				NR		NR	
Muller 1993						NR	
O'Doherty 1998						Pfizer	
Sopena 2004				NR		Pfizer	
Wubbel 1999				NR		Pfizer	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Amin, 1995 USA	Open-label, noncomparative study Multicenter	Patients aged 16 and older with acute sinusitis who had not received antibiotics within 3 days before the start of the study (diagnosis of acute sinusitis was based on s/sx: fever, sinus tenderness, purulent nasal discharge, dullness on transillumination, sinus pain, and headache for fewer than 30 days) (radiographic evidence of sinus infection was required)	azi 500 mg day 1 and 250 mg daily days 2-5 none		clinical response was characterized as cure, improvement, or failure Clinical response was evaluated at visit 2 (days 5-7) and visit 3 (days 12-16)	
Calhoun, 1993 USA, Canada	RCT, single-blind Multicenter	Adult patients with acute maxillary sinusitis (diagnosis confirmed by sinus roentgenogram) with one of the following: pain and/or tenderness in the sinus area, nasal congestion, purulent nasal discharge, sinus headache, facial erythema, or facial swelling. Patients excluded if they had been treated with any of the following: an investigation drug within 4 weeks before the study, a long-acting injectable antibiotic within 6 weeks of the sutdy, or a systemic antibiotic within 3 days of the study. Also excluded were women at risk of pregnancy and patients with chronic maxillary sinusitis; primary fronta or ethmoid sinusitis; hepatic or renal impairmant; a history of hypersensitivity to macrolides, beta-lactam antibiotics, or sympathomimetic amines; or a condition contraindicating the use of oxymetazoline HCL nasal spray.	Clari 500 mg twice daily x7-14 days amox 500 mg three times daily x7-14 days	oxymetazoline nasal spray - 2 sprays of 0.05% into each nostril twice daily for the first 3 days	Clinical cure was determined at visit 3, within 48 hours after finishing their antibiotic therapy, patients were seen again for follow up within 6 weeks if the patients sinusitis worsened or recurred. Results reported together from visit 2 and visit 3. Cure - complete resoluction of s/sx of infections Improvement - s/sx lessened by did not resolve completely Failure - s/sx remianed unchanged or worsened Relapse - worsening or recurrence of s/sx of infection within the 6-week follow-up period Indeterminate - clinical response not evaluable	none
Casiano, 1991 USA	RCT, third-party-blinded Multicenter	Patients aged 16 or older with a clinical diagnosis of an acute episode of bacterial maxillary sinusitis (clinical diagnosis was confirmed by the presence of a bacterial isolate in sinus fluid obtained by transantral aspiration) Causative organism had to be susceptible to both medications. Pregnant and/or lactating females were excluded. Also excluded were patients with known hypersensitivity or intolerance to macrolide or penicillin antibiotics, any history of chronic sinusitis, peptic ulcers or any other condition affecting drug absorption; and treatment within the previous 72 hours with any other antibiotic	azi 500 mg daily on day 1 and 250 mg daily on days 2-5 amox 500 mg three times daily x10 days		Patient response was defined as satisfactory Clinical response evaluated at day 10-13 after initiation of therapy Response defined as satisfactory (if patient was cured, with no s/sx of infection), Improvement (subsidence of s/sx during the study but with incomplete resolution), and unsatisfactory (failure of therapy with no apparent clinical response)	Bacterial eradication was defined as elimination of the initial causative pathogen by day 10-13 Transantral aspiration was only epeated if the patient had not responded to treatment by day 10-13. Eradication was presumed with normalization of sinus opacity on transillumination and radiographs, and resolution of clinical findings.

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to follow up/analyzed**
Amin, 1995 USA	46 males vs 56 females 87 White, 6 Black, 4 Asian, 5 Other		number screened not reported / number eligible not reported / 163 patients enrolled	40 patients withdrawn due to chronic sinusitis / 21 patients lost to follow-up / 102 patients analyzed
Calhoun, 1993 USA, Canada	Gender female - 39/70 clari, 45/72 amox male - 31/70 clari, 27/72 amox mean age - 37 (14-77) clari, 37 (14-74) amox ethnicity not reported	mean duration of therapy for both groups was 14.2±3.2 days no statistically significant difference in any demographic variable	number screened not reported / number eligible not reported / 142 patients enrolled	26 patient excluded from efficacy analysis (noncompliance, premature discontinuation) / number lost to follow-up not reported / 116 analyzed
Casiano, 1991 USA	Gender female - 20/41 azi, 19/37 amox male - 21/41 azi, 18/37 amox mean age - 37.7 (16-60) azi, 38.1 (20-73) amox ethnicity not reported	no other demographics reported	number screened not reported / number eligible not reported / 78 patients enrolled	13 patient were withdrawn due to not meeting entry criteia / 14 in azith and 13 in amox group excluded due to no pathogen or lack of resistance testing / 23 aztih patients analyzed, 15 of amox patients analyzed (38 total)

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Amin, 1995 USA	Visit 2 - 27/102 (26.5%) cure Visit 3 - 56/102 (54/9%) cure	not reported	patient report	64/163 (39.3%) patients reported AE 55/163 (33/7%) with AE considered to be related or possibly related to treatment Most events were GI related (diarrhea, nausea, and gastric pains 1 patient reported urticaria, 1 patient with severe itching of fingers, toes and earlobes, 1 patient experienced exacerbation of underlying COPD	0 patients withdrawn from safety analysis / 0 withdrawals due to adverse events	
Calhoun, 1993 USA, Canada	Cure - 40/55 (73%) clari vs 43/61 (71%) amox (95% CI -14.2-18.7) Improv - 10/55 (18%) clari vs 11/61 (18%) amox failure/relapse - 5/55 (9%) clari vs 7/61 (11%) amox success (cure/improv) - 50/55 (91%) clari vs 54/61 (89%) amox (95% CI -8.6-13.4) P=0.766	not reported	not reported laboratory analysis	total reported AEs not documented GI events - 18 reported clari, 10 reported amox Clari - 6 nausea, 5 abdominal pain, 4 diarrhea, 4 dyspepsia, 1 vomiting Amox - 4 nausea, 4 diarrhea, 1 vomiting, 1 dyspepsia, 1 abdominal pain no clinically significant changes in lab parameters	26 withdrawals / 2 clari and 3 amox withdrew due to adverse events	AEs not well reported Clinical response rate not broken down by visit, reported together
Casiano, 1991 USA	Day 10-13 cure - 17/23 (73.9%) azi, 11/15 (73.3%) amox improv - 6/23 (26.1%) azi, 4/15 (26.7%) amox failure - 0	Day 10-13 - 100% for both arms	Patient report and laboratory analysis (results based on all 78 patients enrolled)	5 patients reported a total of 6 adverse effects Azi - 2/41 (4/9%) - headache and nausea Amox - 3/37 (8.1%) - GI disturbances (diarrhea, loose stools, dyspepsia)	40 total withdrawals / 0 withdrawals due to adverse events	no comparison of severity of infection at baseline

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Clement, 1998 Belgium	RCT, open Single center	adults with clinical signs and symptoms of acute ethmoidal or maxillary sinusitis (diagnosis was confirmed by fibre-optic examination with presence of purulent discharge from the ostium of the affected sinus and CT scan obtained within 72 hours after or before inclusion) Patients with chronic sinusitis or sinusitis believed to be of fungal origin were excluded, as were thosw with known allergies to macrolides or beta-lactam agents, or patients with an infection requiring an intravenous drug. Immunocompromised patients, pregnant or lactating women, those receiving treatment with ergot derivatives, digoxin, cyclosporin, or phenytoin, and those who had received any investigational drug during the preceding month were also excluded	azi 500 mg daily x3 days amox/clav 500/125 mg three times daily x10 days	corticosteroids, vasoconstrictors, mucolytics	Clinical cure was assessed using a clinical score and evaluated at visit 2 (10-14 days) and visit 3 (21-28 days) Outcomes were reported as cure, improved, and failure (based on clinical score, no definition)	Microbiologic outcome was assessed at visit 2 (10-14 days) and visit 3 (21-28 days) Eradication was presumed if no purulent discharge existed, Persistence presumed if purulent discharge present
Dubois, 1993 Canada	RCT, single-blind (investigator) Multicenter	Patients >12 years old, weigh >34 kg, and have a diagnosis of acute maxillary sinusitis based on at least one of the following: sinus pain or tenderness, nasal congestion, purulent discharge, sinus headache, and facial erytherma or swelling. Diagnosis had to be confirmed by a positive maxillary sinus radiograph and positive culture of sinus fluid. Patients excluded if they had: history of sensitivity to macrolide or beta-lactam antimicrobials or sympathomimetic amines; any condition contraindicating the use of oxymetazoline nasal spray; history of chronic maxillary sinusitis; or primary diagnosis of frontal or ethmoid sinusitis. Patients could not have received either a systemic antimicrobial drug within 7 days before the study or a long-acting injectiable antimicrobial within 6 weeks previously. Female patients could not be at risk for pregnancy.	clari 500 mg every 12 hours for a max of 14 days amox/clav 500 mg every 8 hours for a max of 14 days	on days 1-3, patients self administered 0.05% oxymetazoline nasal spray, 2 sprays into each nostril twice daily	determined at visit 3, within 48 hours post-treatment; clinical signs and symptoms were evaluated visit 4 scheduled 14-42 days post-treatment for patients with a clinical response categorized as improvement at visit 3 and for those with sinus films showing no resolution at visit 3 but with a clinical response not categorized as failure clinical response rated as cure (pretreatment s/sx resolved), improvement (improved but no resolved), failure (unimproved or worsened), recurrence (s/sx resolved or improved at visit 3 with reappearance or worsening at 14-42 days post-treatment), indeterminate	eradication (none could be cultured at the end of therapy or there was no clinical indication for culturing), persistence (>1 pathogens present either at visit 3 or at the study's end), relapse (eradication at visit 3 followed by reappearance of the same pathogenduring the 14-42 day follow-up), reinfection (emergence of a new pathogen at visit 3 or 4), or indeterminate evaluated at visit 3 within 48 hours of end of treatment, and visit 4 14-42 days post-treatment

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Clement, 1998 Belgium	mean age 42.1 (azi) vs 38.7 (amox/clav) 37% male and 63% female n=165 (azi) vs 47.2% male and 52.8% female n=89 (amox/clav) ethnicity not reported	No statistically significant difference in any comparator	ns not reported / number eligible not reported / 254 enrolled	14 patients excluded / 10 lost to follow-up / 240 analyzed
Dubois, 1993 Canada	not reported	no statistcally significant differences were observed at baseline in respect to sex, weight, race, or pre-study characteristics no statictically significant difference in disease severity or presenting s/sx	ns not reported / ne not reported / 497 enrolled	237 excluded / lost to fu not reported / 260 analyzed most exclusion was due to absence of pathogen in pretreatment cultures

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Clement, 1998 Belgium	Visit 2 Cure - 90/151 (59.6%) azi vs 47/82 (57.3%) amox/clav Improv - 42/151 (27.8%) azi vs 29/82 (35.4%) amox/clav Failed - 19/151 (12.6%) azi vs 6/82 (7.3%) amox/clav Visit 3 Cure - 102/136 (75%) azi vs 52/74 (70.3%) amox/clav Improv - 17/136 (12.5%) azi vs 10/74 (13.5%) amox/clav Failed - 17/136 (12.5%) azi vs 10/74 (13.5%) amox/clav Relapse - 2/74 (2.7%) amox/clav Response rate for ITT reported as similar, no numbers given	Visit 2 Eradication - 41 (61.5%) azi vs 25 (67.6%) amox/clav Persistence - 22 (34.9%) azi vs 12 (32.4%) amox/clav Visit 3 Eradication - 47 (90.4%) azi vs 26 (83.9%) amox/clav Persistence - 5 (9.6%) azi vs 5 (16.1%) amox/clav	patient report	36 events reported by 29 patients reported AE in azi group 25 events reported by 23 patients reported AE in the amox/clav group Abdominal pain 7 azi, 7 amox/clav; diarrhea 7 azi, 13 amox/clav; nausea 8 azi, 1 amox/clav 5 severe AE in azi vs 3 severe AE in amox/clav No difference in rates of reported events, most commonly reported were diarrhea and nausea	2 patients d/c amox/clav due to adverse events	Microbiological outcomes were reported without secondary cultures taken, just based on the presence or absence of purulent discharge Included patients with ethmoidal sinusitis, most only include maxillary sinusitis patients
Dubois, 1993 Canada	visit 3 cure - clari 85/132 (64%), amox/clav 86/128 (76%) improv - clari 43/132 (33%), amox/clav 33/128 (26%) success (impro+cure) - clari 128/132 (97%), amox/clav 119/128 (93%) failure - clari 4/132 (3%), amox/clav 9/128 (7%) follow-up recurrence - clari 12/132 (9%), amox/clav 5/128 (4%) no statistically significant difference in clinical outcome	visit 3 cure - clari 115/132 (87%), amox/clav 115/128 (90%) failure - clari 16/132 (12%), amox/clav 13/128 (10%) follow-up relapse - clari 5/132 (4%), amox/clav 3/128 (2%) reinfection - clari 2/132 (2%), amox/clav 1/128 (1%) no statistically significant difference was found	not described physician observation patient spontaneous report	clari - 101 patients reported AEs, 51 had gastrointestinal complaints, 7 patients reported severe AEs, dyspepsia with abdominal pain, headache, dysheusia, diarrhea, and nausea amox/clav - 115 patients reported AEs, 90 had gastrointestinal complaints (P<0.001), 16 severe AEs were reported:abdominal pain, diarrhea, migraine, nausea, asthenia, myalgia, headache, otitis media, cerebral ischemia, dizziness, chills, and chest pain Lab abnormalities - elevated bilirubin (1 in each group), elevated GGTP in one amox/clav patient 7 patients in each arm discontinued due to AEs	7 patients in each arem discontinued due to AEs	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	RCT, bacteriological assessment was blinded Multicenter	>17 years old, bacterial infections of the upper respiratory tract. Patients with life-threatening conditions, epiglottidis, cystic fibrosis, or known hypersensitivity to mactrolide antibiotics were excluded, as were those who had received antibiotics in the 48 hours preceding the start of the study, those with any past or present factor which might have affected drug absorption and those with evidence of drug or alcohol abuse. Concurrent administration of warfarin, carbamazepine or ergotamine was not permitted. All women of child-bearing potential were also excluded.	azi 250 mg every 12 hours for day 1, then 250 mg once daily on days 2-5 ery (stearate) 250 mg four times daily x10 days (at one centre 5 pts received 500 mg EES three times daily x10 days; results were not analysed separately)		assessment within 48 hours after the last dose and 7-10 days after final dose Clinical response was assessed as changes compared to baseline in the following: total and differential leucocyte counts, body temperature, pain/tenderness, malaise, erythema, exudates, and radiological findings cured or not cured efficacy calculated from data obtained at the latest examination period 10-15 dys after the start of treatment	bacteriological cultures may have been obtained prior to treatment and at follow-up (48 hours and 7-10 days post treatment) clinical cure organsims were assumed to be eradicated
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	RCT, blinding not reported Multicenter	Patients with presumptive clinical evidence of acute bacterial infection of the frontal and/or maxillary sinus were included in the study. Subjects with hypersensitivity to penicillin antibiotics were excluded, as were pregnant and lactating women; however, all other women of child-bearing potential were included in the study. >17 years old Patients with life-threatening conditions, epiglottidiis, cystic fibrosis, or known hypersensitivity to mactrolide antibiotics were excluded, as were those who had received antibiotics in the 48 hours preceding the start of the study, those with any past or present factor which might have affected drug absorption and those with evidence of drug or alcohol abuse. Concurrent administration of warfarin, carbamazepine or ergotamine was not permitted.	azi 500 mg once daily on day 1, 250 mg once daily on days 2-5 amox 500 mg three times daily x10 days		assessment within 48 hours after the last dose and 7-10 days after final dose Clinical response was assessed as changes compared to baseline in the following: total and differential leucocyte counts, body temperature, pain/tenderness, malaise, erythema, exudates, and radiological findings cure, improved, or failed efficacy calculated from data obtained at the latest examination period 10-15 dys after the start of treatment	bacteriological cultures may have been obtained prior to treatment and at follow-up (48 hours and 7-10 days post treatment) clinical cure organsims were assumed to be eradicated

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	mean age - azi 40.8, ery 39.6 age range - azi 17-70, ery 18-85 azi 105 total - 68 male, 37 female ery 111 total - 64 male, 47 female Sinusitis - azi 65% (68), ery 67% (74) all white european except 1 patient in each group	chronic sinusitis azi 18%, ery 10% puncture and drainage performed in 44% azi and 45% ery groups	ns not reported/ ne not reported/ 216 enrolled	0 withdrawn / 4 azi, 3 ery lost to fu / 209 analyzed
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	mean age - azi 40.4, amox 40.5 age range - azi 17-76, amox 17-76 azi 131 - 62 male, 69 female amox 127 - 66 male, 61 female 2 non-white azi, 1 non-white amox	sinus puncture and drainage performed on 31 (24%) azi and 32 (25%) amox	ns not reported/ ne not reported/ 258 enrolled	14 withdrawn / 14 lost to fu / 244 analyzed

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	azi - 84/101 (83%) ery - 85/108 (79%) P=0.520 sinusitis - azi 85%, ery 75%	eradication - azi 87%, ery 86% P=1.0 azi notably better for Staph aureus (90% vs 63%)	observed by practitioner or spontaneously reported by patient, recorded up to 35 days after the beginning of treatment laboratory safety parameters at baseline, 2 followup visits, and 35 days after the beginning of treatment	azi - 18/105 (17%) reported ae ery - 17/111 (15%) reported ae azi - 19 recored ae, 15 gastrointestinal (diarrhea, nausea), 1 severe ery - 21 recored as, 16 gastrointestinal (diarrhea, abdominal pain), 1 dermal, 3 severe possible drug-related laboratory abnormalities reported in 12% azi, 15% ery	3 withdrawals / 3 due to ae (1 azi, 2 ery)	Study included patients with other upper resperatory infections including tonsillitis, pharynigitis, laryngitis and mixed infections Followup performed at 48 hours after end of treatment and 7-10 days at end of treatment, but efficacy reported as 10-15 days after the start of treatment (azi 6-11 days after completion, ery 1-6 days after completion) Some patients in ery group treated with different salt and different dosing schedule
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	Cure azi - 100/123 (81%) amox - 87/121 (72%) P=0.599 Improved azi - 20/123 (16%) amox - 32/121 (26%) cure plus imporved 98% for azi, 97% for amox	Eradication - azi 94% vs amox 87% P=0.651	observed by practitioner or spontaneously reported by patient, recorded up to 35 days after the beginning of treatment laboratory safety parameters at baseline, 2 followup visits, and 35 days after the beginning of treatment	azi - 6/131 (5%) reported ae amox - 14/127 (11%) reported ae azi - 9 recored ae, 7 gastrointestinal (diarrhea, nausea), 1 dermal, 2 severe amox - 16 recored ae, 10 gastrointestinal (diarrhea), 3 dermal, 3 severe	3 withdrawals / 3 due to ae (3 amox, 0 azi)	

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Haye, 1996 Norway	RCT, double-blind, double-dummy, parallel-goup Multicenter	Patients aged 18-70 years old, with acute maxillary sinusitis (diagnosis based on nasal secretion, purulent at the time of examination, of more than 10 and less than 30 days and/or maxillary sinus tenderness and/or pain of less than 30 days) Diagnosis confirmed by plain radiograph with complete opacity or air-fluid level or mucosal thickness of more than 6 mm. Women who were pregnant, breast-feeding, or of child-bearing potential but not using appropriate contraception were excluded from the study, as were patients with a previous history of intolerance to macrolides, azalides, penicillin, or lactose. Patients with more than 2 prior episodes of sinusitis during the last 12 months were excluded, as were patients who had used antibiotics within the preceding two weeks, those with extensive cariew and/or periodontal disease, those with concurrent acute infections, or those using ergotamine.	azi 500 mg daily x3 days penV (phenoxymethylpenicillin) 1320 mg three times daily x10 days		Clinical response evaluated at visit 2 (3-5 days), visit 3 (10-12 days), and visit 4 (23-27 days) Cure defined as disappearance of all pretreatment symptoms Improvement was considered the partial disappearance of pretreatment s/sx Failure was no change or worsening of s/sx Relapse was initial improvement or disappearance of sx followed by worsening	none

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Haye, 1996 Norway	Gender female - 142/221 azi, 146/217 penV male - 79/221 azi, 71/217 penV mean age - 40.3 (19-71) for azi, 38.6 (20-71) for penV ethnicity not reported	No statistically significant difference in any comparator	number screened not reported / number eligible not reported / 438 patients enrolled	2 patients withdrawn / 0 lost to follow-up / 436 patients analyzed 2 patients not included in visit 2 data but included in all other time points

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Haye, 1996 Norway	Visit 2 Cure - 31/219 (14.2%) azi vs 19/213 (8.9%) penV Improv - 180/219 (82.2%) azi vs 181/213 (85%) penV Failure - 8/219 (3.7%) azi vs 13/213 (6.1%) penV Visit 3 Cure - 128/220 (58.2%) azi vs 111/214 (51.4%) penV Improv - 86/220 (39.1%) azi vs 94/214 (43.5%) penV Failure - 1/220 (0.5%) azi vs 6/214 (2.8%) penV Relapse - 5/220 (2.3%) azi vs 5/214 (2.3%) penV Visit 4 Cure - 174/220 (79.1%) azi vs 163/216 (75.5%) penV Improv - 29/220 (13.2%) azi vs 28/216 (13.0%) penV Failure - 1/220 (0.5%) azi vs 6/216 (2.8%) penV Relapse - 16/220 (7.3%) azi vs 19/216 (8.8) penV Combined cure/improv rate - 92.3% azi, 88.5% penV	not reported	patient report	azi - 89 AEs reported by 73 patients (33%), 65 patients experienced GI effects (33 diarrhea, 17 nausea, 15 abdominal pain) penV - 112 AEs reported by 87 patients (40.1%), 75 patients experienced GI effects (50 diarrhea, 15 nausea, 10 abdominal pain) No statistical significance All events reported as mild or moderate, no withdrawals	2 withdrawals / 0 withdrawals due to adverse events	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Haye, 1998 Norway	RCT, double-blind, double-dummy, parallel-goup Multicenter	Patients, male and female, aged 17-70 years old, with h/o upper repiratory tract infection and with clinical symptoms and signs indicative of but without radiological evidence of acute maxillary sinusitis were recruited Diagnosis was based on the physicians' clinical findings, which had to include one or both of thefollowing symptoms: presence of nasal secretion (purulent at the time of examination) for >10 days and <30 days, and maxillary sinus tenderness and/or pain of <30 days duration. To exclude the presence of empyema, plain radiographs using Waters' projection could not show complete opacity or an air-fluid level and the mucosal thickness must be <6mm as measured at the upper lateral border of the maxillary sinus. women who were pregnant or breast feeding or of child bearing potential but not using appropriate contraception were excluded from the study, as were patients with a history of intolerance to macrolides, azalides, penicillin, or lactose. Patients with more than 2 prior episodes of sinusitis during the last 12 months also were excluded, as were patients who had t	azi 500 mg once daily x3 days placebo once daily x3 days		Evaluation of clinical s/sx on day 3-5, day 10-12, and day 23-27 (symptoms evaluated include nasal secretion, maxillary pain and tenderness, nasal obstruction, and general malaise) Cure - disappearance of all pretreatment symptoms relevant to infection Improvement - partial disappearance of pretreatment signs and symptoms Failure as no change or a worsening of pretreatment syptoms Relapse - initial improvement or disappearance of pretreatment symptoms followed by worsening	none
Henry, 2003 USA	RCT, double-blind, double-dummy, comparative Multicenter	Patients aged 18 years and older with clinical diagnosed with acute bacterial sinusitis (diagnosis confirmed by the presence of either purulent nasal discharge or facial pain/pressure/tightness for more than 7 but fewer than 28 days, X-ray positive for opaxification or air-fluid level or≥ 6mm of mucosal thickening Exclusion criteria included allergy or hypersensitivity to any penicillin or macrolide antibiotic, a history of chronic sinusitis, history of sinus surgery other than for diagnostic procedure, and treatment with systemic histamine receptor antagonists	azi 500 mg daily x3 days azi 500 mg daily x6 days amox/clav (liquid) 500/125 mg three times daily x10 days		Clinical success rate At day 8-15 (end of treatment) evaluated for improvement or cure At day 22-36 (end of study) evaluated for cure Cure defined as resolution of s/sx to the level that existed prior to theoccurrence of the acute illness with no worsening i the radiographic appearance of the sinuses and without requirement of antibiotics. Improvement defined as partial but imcomplete resolution of the s/sx,and no requirement for additional antibiotic use Failure defined as persistence of one or more s/sx or appearance of new signs or symptoms and/or need for additional antimicrobials or change in antimicrobial therapy	none

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Haye, 1998 Norway	mean age - azi 40.2, placebo 43.2 age range - azi 21-70, placebo 18-68 azi (87) - 18 male, 69 female placebo (82) - 26 male, 56 female ethnicity not reported	no difference in demographic variables, most patients had moderate symptoms	ns not reported / ne not reported / 169 enrolled	0 withdrawn / 0 lost to fu / 169 analyzed
Henry, 2003 USA	Mean age 40.2 (18-76) azith 3day, 41.3 (18-80) azi 6 day, 42.4 (18-84) amox/clav Male/Female ratio - 123/189 (n=312) azi 3day, 124/187 (n=311) azi 6day, 134/179 (n=313) amox/clav Ethnicity - 271 White, 20 Black, 2 Asian, 19 Other (azi 3day); 261 White, 18 Black, 9 Asian, 23 Other (azi 6day); 274 White, 19 Black, 3 Asian, 17 Other (amox/clav)		number screened not reported / number eligible not reported / 941 patients enrolled	21 patients excluded for ITT either for center ineligibility or not meeting entry criteria / 0 lost to follow-up / 920 analyzed in ITT 799 patients analyzed in PP at EOT and 794 EOS 936 analyzed for safety

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Haye, 1998 Norway	3-5 days cure - azi 12/84 (14.3%), placebo 7/81 (8.6%) Improvement - azi 67/84 (79.9%), placebo 64/81 (79.0%) failure - azi 5/84 (6%), placebo 10/81 (12.4%) 10-12 days cure - azi 50/86 (58.1%), placebo 26/82 (31.7%) improv - azi 30/86 (34.9%), placebo 46/82 (56.1) failure - azi 2/86 (2.3%), placebo 6/82 (8.5%) relapse - azi 4/86 (4.7%), placebo 3/82 (3.7%) 23-27 days cure - azi 69/87 (79.3%), placebo 55/82 (67.1%) improv - azi 9/87 (10.3%), placebo 7/82 (20.7%) failure - azi 2/87 (2.3%), placebo 6/82 (7.3%) relapse - azi 7/87 (8%), placebo 4/82 (4.9%) only statistical significance is cure rate at 10-12 day visit P=0.001	not reported	not described spontaneous patient report	azi - 28 AEs reported by 24 (27.6%) patients - mostly gastrointestinal, diarrhea 11, nausea 7, abdominal pain 3 placebo - 21 AEs reported by 15 (18.3%) patients - mostly gastrointestinal, diarrhea 5, nausea 1, abdominal pain 1 1 severe case reported in azi group no discontinuations in either group difference in AEs reported was not statistically significant	none	patients in this study did not meet true definition of sinusitis according to radiographic findings, did meet clinical s/sx definition
Henry, 2003 USA	Clinical success at end of treatment (cure or improvement) ITT - 268/303 (88.4%) (97.5% CI -3.0-9.4) for azi 3day, 265/298 (88.9%) (97.5% CI -2.5-9.9) for azi 6day, 248/291 (85.2%) for amox/clav PP - 239/269 (88.8%) (97.5% CI -2.7-10.5) for azi 3day, 242/271 (89.3%) (97.5% CI -2.2-10.9) for azi 6day, 220/259 (84.9%) for amox/clav Clinical success at end of study (cure) ITT - 213/298 (71.5%) (97.% CI -8.4-8.3) for azi 3day, 218/294 (74.1%) (97.5% CI -5.6-10.9) for azi 6 day, 206/288 (71.5%) amox/clav PP - 195/272 (71.7%) (97.% CI -8.5-9.2) for azi 3day, 199/271 (73.4%) (97.5% CI -6.7-10.9) for azi 6 day, 179/251 (71.3%) amox/clav	not reported	patient report and physician observation	Reported AEs azi 3day - 97/312 (31/1%) azi 6day - 117/311 (37.6%) amox/clav - 160/313 (51.1%) Diarrhea, nausea and flatulence were the most commonly reported adverse events in all 3 groups azi 3day - 53/312 (17%) diarrhea, 23/312 (7.4%) nausea, 17/312 (5.4%) flatulence azi 6day - 66/311 (21.2%) diarrhea, 27/311 (8.7%) nausea, 11/311 (3.5%) flatulence amox/clav - 101/313 (32.3%) diarrhea, 38/313 (12.1%) nausea, 6/313 (1.9%) flatulence	7/312 (2.2%) discontinued in azi 3day 11/311 (3.5%) discontinued in azi 6day 28/313 (8.9%) discontinued in amox/clav	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Karma, 1991 Finland, Sweden	RCT, single-blind Multicenter	Outpatients suffering fro acute maxillary sinusitis. Suggestive sinus X-ray and at least one of the following clinical symptoms: pain and/or tenderness int eh sinus area, nasal congestion, purulent nasal discharge, sinus headache, facial erythema or facial swelling. Diagnosis was confirmed by the presence of fluid demonstrated during antral puncture, in bilateral cases usually from the most affected sinus. Pathogens cultured from sinus fluid had to be susceptible to both the study antibiotics. Patients with renal impairment or hepatic disease, chronic maxillary sinusitis, or frontal or ethmoid sinusitis, and those at risk of pregnancy were excluded from the study. Patients with history of hypersensitivity to macrolides and beta-lactam antibiotics, or sympathomimetic amines, or taking medications that would negate the effectiveness of the study drugs were also excluded.	clari 500 mg every 12 hours x9-11 days amox 500 mg every 8 hours x9-11 days	0.05% oxymetazoline nasal spray twice daily for first 3 days	Cure - resolution of pre-treatment s/sx of infection Improv - improvement but not resolution of pre-treatment s/sx failure - no improvement in pre-treatment s/sx clinical outcome observed at visit 2 (day 4-6 of therapy) and visit 3 (within 48 hours of completion of therapy)	Bacteriologic response was based on the eradication of causative pathogens obtained at the pretreatment culture at the end of treatment. In this respect, cases in which complete clinical recovery had occurred were not re-cultured but were assumed to be bacteriologically negative
Klapan, 1999 Croatia	Randomized, open, comparative Single center	Patients with acute sinusitis >15 years old Sinusitis diagnosis establised based on clinical findings (s/sx consistent with sinusitis which lasted less than 4 weeks), sinus radiography (opacities, mucosal thickening $\geq$4mm, or fluid levels in affected sinuses), and nasal endoscopy (complete obstruction of the ostiomeatal complex or partial obstruction with purulent discharge) Pregnant and lactating women wre excluded, as well as patients with hypersensitivity to the study drugs, severe renal or hepatic impairment, gastrointestinal disorders that could affect drug absorption, immunodeficiency, clinically significant viral infection, and subchronic or chronic sinusitis. Also, excluded were patients who had received more than one daily dose of any antibacterial treatment within 7 days before enrollment.	azi 500 mg daily x3 days amox/clav 500/125 mg every 8 hours x10 days		Clinical response evaluated at end of treatment day 10-12 and at follow-up 4 weeks after initiation of treatment Response was defined as either cure complete disappearance of s/sx of sinusitis, clinical score <1), improvement (only partial disappearance of s/sx but without need for additional antimicrobial therapy), failure (persistence or progression of s/sx that required additional antimicrobial therapy), or relapse (a reappearance of s/sx during follow-up).	Bacteriologic response evaluated at 72 hours after treatment initiation Bacteriologic reponse defined as eradication (the culture of sinus aspirate was positive at baseline and negative after 72 hours of treatment), presumed eradication (the culture of sinus aspirate was positive at baseline and a control culture was not performed due to complete clinical response), persistence (the culture of sinus aspirate was still positive after at least 72 hours of treatment), or superinfection (the emergence of a new pathogen in the culture of sinus aspirate after at least 72 hours of treatment).

Evidence table 3. Summary of sinusitis trials

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Karma, 1991 Finland, Sweden	Gender female - clari 5/50, amox 6/50 male - clari 45/50, amox 44/50 Mean Age - clari 29.0, amox 30.2 Age range - clari 17-66, amox 18-69	No statistically significant difference in any comparator	ns not reported / ne not reported / 100 enrolled	32 patients excluded (17 clari, 15 amox) / 0 patients lost to fu / 68 analyzed
Klapan, 1999 Croatia	100 patients aged 15 to 50 Mean age - azi 33, amox/clav 32 Gender female - 10/50 azi, 13/50 amox/clav male - 40/50 azi, 37/50 amox/clav ethnicity not reported	groups were comparable with respect to case histories and baseline clinical data	number screened not reported/number eligible not reported/100 enrolled	3 patients excluded from analysis due to violating inclusion criteria/no patients withdrew/ no patients lost to follow-up/97 patients analyzed

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Karma, 1991 Finland, Sweden	visit 3 cure - clari 19/33 (59%), amox 26/35 (74%) improv - clari 10/33 (31%), amox 6/35 (17%) failure - clari 3/33 (9%), amox 3/35 (9%) visit 4 cure - clari 19/23 (83%), amox 22/26 (85%) improv - clari 1/23 (4%), amox 0/26 failure - clari 3/23 (13%), amox 4/26 (15%)	Eradication - clari 32/36 (89%), amox 35/38 (92%) following the end of treatment (undefined)	not reported	clari 16% reported AEs amox 26% reported AEs GI - clari 7 (14%), amox 6 (12%)	1 withdrawal due to AEs (amox)	When clinical cure reported there were several patients not included with the label "not determined", there was no explanation why these patients results were missing.
Klapan, 1999 Croatia	10-12 days: cure - 40/47 (95%) azi vs 35/47 (74%) amox/clav (P=0.012) improv - 3/47 (5%) azi vs 12/47 (26%) amox/clav follow-up: cure - 42/43 (98%) azi vs 42/46 (91%) amox/clav (P>0.05) Failure: 3 (7%) amox/clav group Relapse at follow-up: 1/43 (2%) azi, 1/46 (2%) amox/clav Faster resolution of s/sx: azi group (significantly lower clinical score at day 4 and day 10-12) (P=0.001 and P=0.042)	no significant difference in bacteriologic response among the groups Eradication confirmed - 20/23 azi, 20/24 amox/clav Eradication presumed - 3/23 azi, 1/24 amox/clav Persistence - 2/24 amox/clav patients relapse - 1/24 amox/clav	patient report	2 (4%) azithro patients reported mild, transient, GI disturbances (nausea and vomiting) 5 (10%) amox/clav patients reported nausea	0 withdrawals/0 withdrawals due to adverse events	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Marchi, 1990 Italy	Open Multicenter	outpatients over the age of 18 who were diagnosed with acute maxillary sinusitis suitable for oral antibiotic therapy. Patients had at least one of the following s/sx: pain and/or tenderness in the sinus area, nasal congestion, purulent nasal discharge, sinus headache, facial erythema or facial swelling. Diagnosis was confirmed by sinus X-ray or microbiological culture obtained at the initial visit. Pathogens had to be detectable to both study drugs. Patients were ineligible if they had chronic maxillary sinusitis, frontal or ethmoidal sinusitis, were undergoing concurrent treatment with a systemic decongestant and/or antihistamine or monoamine oxidase inhibitor, were using other therapies that would interfere with the results of the study, or were sufering from medical conditions that could be adversely affected by the antibiotic therapy or could affect patient reactions to the therapy.	clari 500 mg twice daily x 14 days amox 1000 mg twice daily x14 days	0.05% oxymetazoline nasal spray twice daily for first 3 days	visit 4 - 48 hours after completion of therapy visit 5 - up to 6 weeks after for patients not assigned a clinical response of cure at visit 4 cure - resolution of pretreatment s/sx of the infection improv - improvement but not complete resolution of pretreatment s/sx failure - no improvement in pre-treatment s/sx indeterminate - clinical response to therapy could not be determined	visit 4 eradication persistence indeterminate
Murray, 2000 USA, Canada	RCT, double-blind, parallel-goup Multicenter	Male and female outpatients aged >12 years with a presumptive diagnosis of acute maxillary sinusitis supported by confirmatory sinus radiographs obtained within 72 hours before treatment were enrolled. S/sx included facial pain, pressure, tightness over maxillary sinuses, or purulent nasal discharge for at least 7 days before and not longer than 28 days before the pretreatment visit. Patients were excluded if they had evidence of chronic maxillary sinusitis, a diagnosis of frontal, ethmoid, or sphenoid sinusitis; a history of hypersensitivity to sympathomimetic amines or macrolides or conditions known to alter immune function. Patient were also exluded if they had used a systemic antibiotic within 3 weeks before study initiation; had received a long-acting injectable antibiotic within 30 days of study initiation; were receiving immunosuppressive drugs; had significant renal or hepatic impairment; or were pregnant or lactating.	clari ER 1000 mg once daily x14 days clari 500 mg twice daily x14 days	0.05% oxymetazoline nasal spray twice daily for first 3 days	Test-of-cure clinical response rate was determined on study days 24-31 cure - pretreatment s/sx of infectio had resolved ore improved at eh test-of-cure or 4-week posttreatment visit, no worsening was observed in the radiographic appearance of the sinuses, and no further antimicrobial ttherapy was required failure - pretreatment s/sx of infection did not improve or worsened, new symptoms may have appeared, and the patient required additional antimicrobial therapy at the tes-of-cure or 4-week posttreatment visit indeterminate - clinical response to therapy could not be determined	none
Ng, 2000 China	Peds azi vs amox/clav RCT, single-blind Single center	Children age 5-16, duration of nasal symptoms of blockage and/or discharge for between 30 days and 120 days, abnormal sinux X-rays that showed mucosal thickening $\geq$6 mm or complete opacification or air-fluid level in one o both antra	azi 10 mg/kg/day x3 days amox/clav 312 mg three times daily (6-12 yo) x14 days amox/clav 375 mg three times daily (>12 yo) x14 days	budesonide nasal spray 50 mcg/nostril twice daily for duration of study (91 days)	treatment failure measured at the end of treatment relapse measured at 90 days from end of treatment	

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Marchi, 1990 Italy	Gender female - 21/61 clari, 25/59 amox male - 40/61 clari, 34/59 amox mean age - 48 clari, 47 amox age range - 19-61 clari, 19-76 amox	No statistically significant difference in any comparator	ns not reported / ne not reported / 120 enrolled	6 patients excluded from analysis / number lost to fu not reported / 114 analyzed
Murray, 2000 USA, Canada	Gender female - ER 93/142 (65%), IR 88/141 (62%) male - ER 49/142 (35%), IR 53/141 (38%) Mean age - ER 41.9, IR 41.0 Age range - ER 13-78, IR 15-73 Ethnicity White - ER 119/142 (84%), IR 127/141 (90%) Black - ER 17/142 (12%), IR 10/141 (7%) Other - ER 6/142 (4%), IR 4/141 (3%)	No statistically significant difference in any comparator	ns not reported / ne not reported / 283 enrolled	38 patients deemed nonassessable / number lost to fu not reported / 245 analyzed
Ng, 2000 China	mean age 9.3 vs 8.7 (azithromycin vs amoxicillin/clavulanate) male to female ratio 13:7 vs 14:7 (azithromycin vs amoxicillin/clavulanate) ethnicity not reported		number screened not reported/number eligible not reported/42 enrolled	number withdrawn not reported/1 lost to follow-up/41 analyzed

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Marchi, 1990 Italy	visit 4 cure - 58% clari, 49% amox improv - 33% clari, 35% amox failure - 8.8% clari, 15.8% amox visit 5 cure - 78.9% clari, 85% amox improv - 15.8% clari, 10% amox overall clinical success - 91% clari, 84% amox	eradication - 89% clari, 93% amox	not reported	2 clari patients reported AEs - 1 urticaria, 1 nausea/vomiting 4 amox patients reported AEs - 1 urticaria, , 1 nausea, 1 pruritus, 1 dyspepsia	0 withrawals due to AEs	the microbiologic evaluation and results were not well described and were difficult to explain
Murray, 2000 USA, Canada	Cure in assessable patients clari ER 104/122 (85%) (95%CI 78 91), IR 97/123 (79%) (95%CI 71-86) difference not statistically significant ITT - clinical response rates were similar, but not reported No statistically significant difference between response rates in the assessable patients and ITT	not reported	physician examination laboratory analysis patient self report	AEs reported - ER 45/142 (32%), IR 40/141 (28%) P=0.60 abnormal taste - 10% in each group diarrhea - ER 6%, IR 8% nausea - ER 5%, IR 9% no statistically significant difference in the incidence of AEs	ER - 5/142 (4%) IR - 11/141 (8%) P=0.13 GI or abnormal taste - ER 2/142 (1%), IR 10/141 (7%) P=0.02	compliance was higher in the clarithromycin ER group in both the ITT and treated patients: 97% vs 92% (P=0.02) and 97% vs 91% (P=<0.01)
Ng, 2000 China	Treatment Failure - 6 (azithromycin), 5 (amox/clav) 0.86 (95% CI 0.44-1.60) Recurrence - 0 (azithromycin), 4 (amox/clav) 2.70 (95% CI 0.46-16.00)		patient report	1 patient from each group reported mild epigastric discomfort, self-limited, required no treatment	1/22 withdrew from amox/clav group no withdrawals due to adverse effects	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment - Clinical Cure	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Riffer, 2005 USA, Canada, Greece, Hungary, Itly, Lithuania, Poland, Romania, Spain	RCT, single-blinded (investigator blinded) Multicenter	Ambulatory patients at least 12 years old with a diagnosis of acute, uncomplicated bacterial sinusitis. The diagnosis was based on the presence of: opacification or an air/fluid level in a sinus radiograph or CT scan of maxillary sinuses, purulent nasal discharge, and at least two relevant signs and symptoms (facial pain or facial pressure over one or both maxillary sinus areas, nasal congestion, and fever) lasting longer than 7 days but no longer than 28 days prior to the screening visit. Patients with chronic sinusitis, anatomic abnormality involving maxillary sinuses were excluded. Also excluded were those with an uncontrolled, clinically significant co-morbid disease, pregnant or lactating females, and immunocompromised patients. Use of systemic antibiotics within 14 days before initiation of study drug or concurrently with study drug was prohibited, immunosuppressant coadministration and topical or inhaled corticosteroids were prohibited.	clari ER 1000 mg once daily amox/clav 875/125 mg twice daily x14 days	Use of decongestants, antihistamines, and other symptomatic relief medications was not restricted	Clinical response was evaluated at day 16-18 (test-of-cure) for clinical cure or failure and at day 24-31 (follow-up) for sustained cure or recurrence. Cure defined as resolution or improvement in purulent nasal discharge and at least one additional sinusitis s/sx observed at baseline, with no worsening in the remaining s/sx and no additional requirement for antimicrobial therapy. Failure defined as worsening of at least one of the sinusitis s/sx observed at baseline ore appearance of new s/sx at the test-of-cure visit and the necessity of additional antimicrobial therapy. Sustained cure was defined as continued improvement or no worsening of sinusitis s/sx and no worsening in the radiographic appearance of the sinus. Recurrence was defined as s/sx recurring an time prior to the follow up visit and additional antimicrobial therapy was warranted	Microbiologic cure was assessed at test-of-cure visit (day 16-18). Eradication was defined as the absence of the original infecting pathogens in a repeat sinus aspirate or endoscopic culture. Persistence was defined as appearance of the original pathogen on repeat aspirate or endoscopic culture. Presumed eradication was if the patient was classified as clinical cure and no repeat culture was available. Presumed persistent was if the patient was classified as clinical failure, but no culture was available. New infection was defined a isolation of a new pathogen at post treatment from a repeat sinus aspirate or endoscopic culture.
Stefansson, 1998 Iceland, South Africa, Czech Republic, Finland, Israel, Jordan, Poland, Sweden	RCT, double-blind, parallel-group Multicenter	Male or female patients aged 18 years or older, presenting with a clinical diagnosis of sinusitis with the initial onset of sx within 30 days of study entry. Radiographic evidence of opacification and/or air-fluid level in the maxillary sinus was required. Patients had at least 2 of the following: rhinorrhoea, nasal congestion, facial pain	clari 250 mg twice daily x10 days cefuroxime 250 mg twice daily x10days		Clinical cure defined as clinical s/sx improved or resolved at post-treatment and absent at follow-up. Post-treatment evaluation at day 1-3 after completion of treatment Follow-up evaluation at day 28-35 post-treatment	
von Sydow, 1984 Sweden	RCT, double-blind Single-center	patients without known allergic or vasomotor rhinitis, having suffered from fever and purulent nasal discharge and/or other symptoms of acute maxillary sinusitis for not more thatn four weeks, were accepted. Clinical examination confirmed observation of pus in the nasal caity and other signs of maxillary sinus infection the diagnosis was confirmed radiologically. Completely opaque sinuses were aspirated for the demonstration of pus.	ery base 500 mg twice daily penV (phenoxymethylpenicillin potassium) 1600 mg twice daily	oxymetazoline dose not specified	recovered - no clinical symptoms, normalized nasal mucous membranes improved - negligeable clinical symptoms and/or catarrhal mucous membranes without purulent discharge failure - clinical symptoms of infection and/or purulent discharge	none

Author, Year Country Trial Name	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/analyzed
Riffer, 2005 USA, Canada, Greece, Hungary, Itly, Lithuania, Poland, Romania, Spain	Gender female - clari 127/221 (57%), amox/clav 116/216 (54%) male - clari 94/221 (43%), amox/clav 100/216 (46%) Mean Age - clari 37.2, amox/clav 36.8 Age range - clari 13-75, amox/clav 14-79 Race Caucasian - clari 216/221 (98%), amox/clav 210/216 (97%) Black - clari 2/221 (1%), amox/clav 1/216 (<1%) Other - clari 3/221 (1%), amox/clav 5/216 (2%)	No statistically significant difference in any comparator	ns not reported / ne not reported / 437 enrolled	Bacteriological ITT - 219 excluded / lost to fu not reported / 218 analyzed Clincal ITT - 14 excluded / lost to fu not reported / 423 analyzed Clinically and bacteriologically evaluable - 328 excluded / 5 lost to fu / 109 analyzed Clinically evaluable - 64 excluded / 3 lost to fu / 373 analyzed
Stefansson, 1998 Iceland, South Africa, Czech Republic, Finland, Israel, Jordan, Poland, Sweden	72 males and 113 females - clari 85 males and 100 females - cef mean age 37.2 - clari mean age 36.5 - cef Ethnicity - 171 White, 1 Black, 8 Asian - clari; 170 White, 1 Black, 11 Asian - cef		number screened not reported / number eligible not reported / 370 patients enrolled	39 patients discontinued from study / 19 lost to follow-up / 370 analyzed in ITT analysis
von Sydow, 1984 Sweden	Gender female - ery 32/50, penV 39/50 male - ery 18/50, penV 11/50 Mean age - ery 33, penV 36 age range not reported ethnicity not reported	number of patients with both sinuses affected was somewhat greater in the penV group (32 vs 25)	ns not reported / ne not reported / 100 enrolled	9 excluded / number lost to fu not reported / 91 analyzed

Author, Year Country Trial Name	Clinical Cure	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Riffer, 2005 USA, Canada, Greece, Hungary, Itly, Lithuania, Poland, Romania, Spain	Clinical cure rate evaluable - clari 184/188 (98%), amox/clav 179/185 (97%) - 95%CI (-2.4, 4.7) ITT - clari 194/214 (91%), amox/clav 185/209 (89%) - 95%CI (-3.9, 8.2) Clinical cure rate at follow-up evaluable - clari 172/180 (96%), amox/clav 164/171 (96%) - 95%CI (-4.9, 4.2) ITT - clari 181/194 (93%), amox/clav 170/185 (92%) - 95%CI (-4.2, 7.0)	Bacteriologic cure evaluable - clari 52/55 (95%), amox/clav 53/54 (98%) - 95%CI (-11.6, 4.4) ITT - clari 55/61 (90%), amox/clav 54/61 (89%) - 95%CI (-10.2, 13.5) Eradication in evaluable patients clari 61/65 (94%), amox/clav 61/62 (98%) P=0.366	not reported lab specimens collected at baseline and test-of-cure visit	overall frequency - clari 48/221 (22%), amox/clav 43/216 (20%) diarrhea - clari 4%, amox/clav 6% abnormal taste - clari 11%, amox/clav 1% P<0.001 vaginitis - clari 2%, amox/clav 8% P=0.028	4 clari patients withdrew due to AEs 6 amox/clav patients withdrew due to AEs only lab change noted, 2 patients in amox/clav had increased transaminase levels	
Stefansson, 1998 Iceland, South Africa, Czech Republic, Finland, Israel, Jordan, Poland, Sweden	Post-treatment - 172 (93%) clari vs 169 (91%) cef Follow-up - 143 (77%) clari vs 137 (74%) cef	not reported	patient report	18/185 in clari and 17/185 in cef reported AE 8 clari and 13 cef reported GI effects 3 clari - infection of inflammation of reproductive tract 3 serious events in clari - maxillary antral abscess, convulsions, and collapse during local anaesthesia	39 withdrawals / 2 withdrawals due to AE (clari)	
von Sydow, 1984 Sweden	recovered/improved - ery 46/47 (98%), penV 40/44 (91%)	not reported	patient spontaneous report	AEs reported - ery 19/50, penV 10/50 ery - 1 itching, 3 fatigue, 6 epigastric pain, 1 epigastric pain and vomiting, 3 nausea, 5 diarrhea penV - 1 urticaria, 1 swollen eye-lids, 1 fatigue, 1 epigastric pain, 1 epigastric pain and vomiting, 6 diarrhea	ery - 1 withdrawal (epigastric pain and vomiting) penV - 1 withdrawal (urticaria)	results not well reported, no indicatio of why patients weren't included in analysis, no report of days of therapy, no indication of when (what day) clinical results were recorded

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Calhoun, 1993 USA, Canada	method NR	NR	yes	yes	NR	yes	no	no	no	no	yes	fair
Casiano, 1991 USA	yes	yes	yes	yes	NR	yes	yes	no	no	no	yes	fair

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Calhoun, 1993 USA, Canada	142 enrolled	Patients excluded if they had been treated with any of the following: an investigation drug within 4 weeks before the study, a long-acting injectable antibiotic within 6 weeks of the study, or a systemic antibiotic within 3 days of the study. Also excluded were women at risk of pregnancy and patients with chronic maxillary sinusitis; primary frontal or ethmoid sinusitis; hepatic or renal impairmant; a history of hypersensitivity to macrolides, beta-lactam antibiotics, or sympathomimetic amines; or a condition contraindicating the use of oxymetazoline HCL nasal spray.	no	no	yes	Abbott - industry	good
Casiano, 1991 USA	78 enrolled	Pregnant and/or lactating females were excluded. Also excluded were patients with known hypersensitivity or intolerance to macrolide or penicillin antibiotics, any history of chronic sinusitis, peptic ulcers or any other condition affecting drug absorption; and treatment within the previous 72 hours with any other antibiotic	no	no	yes	Pfizer - Industry	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Clement, 1998 Belgium	method NR	NR	yes	yes	NR	no	no	no	no	yes	no	fair
Dubois, 1993 Canada	method NR	NR	yes	yes	NR	yes	no	no	no	no	yes	fair

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Clement, 1998 Belgium	254 enrolled	Patients with chronic sinusitis or sinusitis believed to be of fungal origin were excluded, as were thosw with known allergies to macrolides or beta-lactam agents, or patients with an infection requiring an intravenous drug. Immunocompromised patients, pregnant or lactating women, those receiving treatment with ergot derivatives, digoxin, cyclosporin, or phenytoin, and those who had received any investigational drug during the preceding month were also excluded	no	no	yes	Pfizer - Industry	fair
Dubois, 1993 Canada	497 enrolled	Patients exculed if they had: history of sensitivity to macrolide or beta-lactam antimicrobials or sympathomimetic amines; any condition contraindicating the use of oxymetazoline nasal spray; history of chronic maxillary sinusitis; or primary diagnosis of frontal or ethmoid sinusitis. Patients could not have received either a systemic antimicrobial drug within 7 days before the study or a long-acting injectiable antimicrobial within 6 weeks previously. Female patients could not be at risk for pregnancy.	none reported	NR	yes	Abbott - industry	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	yes	no	yes	yes	NR	no	no	no	no	no	yes	fair
Haye, 1996 Norway	yes	NR	yes	yes	NR	yes	yes	no	no	no	yes	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Felstead, 1991 Britain, Europe (Belgium, Denmark, Finland, FRG, Norway, Sweden)	258 enrolled	patients with life-threatening conditions, epiglottidiiis, cystic fibrosis, or known hypersensitivity to mactrolide antibiotics were excluded, as were those who had received antibiotics in the 48 hours preceding the start of the study, those with any past or present factor which might have affected drug absorption and those with evidence of drug or alcohol abuse. Concurrent administration of warfarin, carbamazepine or ergotamine was not permitted. All women of child-bearing potential were also excluded	no	NR	yes	Pfizer - Industry	good
Haye, 1996 Norway	438 enrolled	Women who were pregnant, brast-feeding, or of child-bearing potential but not using appropriate contraception were excluded from the study, as were patients with a previous history of intolerance to macrolides, azalides, penicillin, or lactose. Patients with more than 2 prior episodes of sinusitis during the last 12 months were excluded, as were patients who had used antibiotics within the preceding two weeks, those with extensive cariew and/or periodontal disease, thos wit concurrent acute infections, or those using ergotamine.	no	no	yes	NR	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Haye, 1998 Norway	yes	NR	yes	yes	NR	yes	yes	no	no	yes	no	good
Henry, 2003 USA	method NR	NR	yes	yes	NR	yes	yes	no	no	yes	yes	good
Karma, 1991 Finland, Sweden	method NR	NR	yes	yes	NR	yes	no	no	no	no	yes	fair

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Haye, 1998 Norway	169 enrolled	To exclude the presence of empyema, plain radiographs using Waters' projection could not show complete opacity or an air-fluid level and the mucosal thickness must be <6mm as measured at the upper lateral border of the maxillary sinus. women who were pregnant or breast feeding or of child bearing potential but not using appropriate contraception were excluded from the study, as were patients with a history of intolerance to macrolides, azalides, penicillin, or lactose. Patients with more than 2 prior episodes of sinusitis during the last 12 months also were excluded, as were patients who had taken antibiotics within the preceding 2 weeks, those having extensive caries and/or periodontal disease, concurrent acute infections, or those using ergotamin.	no	NR	yes	PFIZER INDUSTRY	Patients similar to those seen in outpatient practice, difficult to compare across trials due to lack of radiographic confirmation
Henry, 2003 USA	936 enrolled	Exclusion criteria included allergy or hypersensitivity to any penicillin or macrolide antibiotic, a history of chronic sinusitis, history of sinus surgery other than for diagnostic procedure, and treatment with systemic histamine receptor antagonists	no	no	yes	Pfizer - Industry	good
Karma, 1991 Finland, Sweden	100 enrolled	Patients with renal impairment or hepatic disease, chronic maxillary sinusitis, or frontal or ethmoid sinusitis, and those at risk of pregnancy were excluded from the study. Patients with history of hypersensitivity to macrolides and beta-lactam antibiotics, or sympathomimetic amines, or taking medications that would negate the effectiveness of the study drugs were also excluded.	no	no	yes	NR	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Klapan, 1999 Croatia	method NR	NR	yes	yes	NR	no	no	no	no	no	yes	fair
Marchi	no	NR	yes	yes	no	no	no	no	no	no	yes	poor
Murray	method NR	NR	yes	yes	yes	yes	yes	no	no	yes	yes	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Klapan, 1999 Croatia	100 enrolled	Pregnant and lactating women wre excluded, as well as patients with hypersensitivity to the study drugs, severe renal or hepatic impairment, gastrointestinal disorders that could affect drug absorption, immunodeficiency, clinically significant viral infection, and subchronic or chronic sinusitis. Also, excluded were patients who had received more than one dily dose of any antibacterial treatment within 7 days before enrollment.	no	no	yes	NR	good
Marchi	120 enrolled	Patients were ineligible if they had chronic maxillary sinusitis, frontal or ethmoidal sinusitis, were undergoing concurent treatment with a systemic decongestant and/or antihistamine or monoamine oxidase inhibitor, were using other therapies that would interfere with the results of the study, or were sufering from medical conditions that could be adversely affected by the antibiotic therapy or could affect patient reactions to the therapy.	no	no	yes	NR	fair
Murray	283 enrolled	Patients were excluded if they had evidence of chronic maxillary sinusitis, a diagnosis of frontal, ethmoid, or sphenoid sinusitis; a history of hypersensitivity to sympathomimetic amines or macrolides or conditions known to alter immune function. Patient were also exluded if they had used a systemic antibiotic within 3 weeks before study initiation; had received a long-acting injectable antibiotic within 30 days of study initiation; were receiving immunosuppressive drugs; had significant renal or hepatic impairment; or were pregnant or lactating.	no	no	yes	Abbott - industry	good

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Riffer, 2005 USA	method NR	NR	yes	yes	NR	yes	no	no	no	yes	yes	good
von Sydow, 1984 Sweden	method NR	NR	yes	yes	NR	yes	yes	no	no	no	NR	poor

Evidence table 4. Quality assessment of sinusitis trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Riffer, 2005 USA	437 enrolled	Patients wit chronic sinusitis, anatomic abnormality involving maxillary sinuses were excluded. Also excluded were those with an uncontrolled, clinically significant co-morbid disease, pregnant or lactating females, and immunocompromised patients. Use of systemic antibiotics within 14 days before initiation of study drug or concurrently with study drug was prohibited, immunosuppressant coadministration and topical or inhaled corticosteroids were prohibited.	no	no	yes	Abbott - industry	good
von Sydow, 1984 Sweden	100 enrolled	NR	no	no	yes	NR	poor

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Adler, 2000 USA, Canada	Randomized, double-blind, parallel-group, phase 3 Multicenter	Age ≥ 12 yr AECB: clinical (productive cough w/ purulent sputum, fever, hoarseness, wheezing), bacteriologic criteria Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	clari ER 1000 mg qd + placebo of IR x 7 days clari IR 500 mg bid + placebo of ER x 7 days	Not described	Eval at day 0 (w/in 48h entry), day 8-10 (w/in 48h study completion), day 19-21 (TOC) Clinical signs, sx assessed at each visit: cough, sputum pruduction, rales/crackling, egophony, rigors, rhonchi/wheezing, substernal and pleuritic pain, pleural effusion, headache, coryza, hoarseness, sore throat, dyspnea, fever, volume sputum production, sputum appearance Outcomes: cure: pre-tx signs, sx resolved or improved at TOC visit and no further ABX required failure: pre-tx signs, sx not improved or worsened and pt required additional ABX at TOC visit indeterminate: inability to eval response
Bradbury, 1993 Ireland, Germany	Randomized, open-label Multicenter	AIECB dx'd by clinical hx, physical findings, and, where possible, organism isolation Exclusion: cystic fibrosis, chronic diarrhea, peptic ulcer dx, any dx likely to affect drug absorption, terminally ill, pts receiving ergotamine, carbamazepine, or digitalis, drug- or alcohol-dependency, use of ABX w/in prior 2 weeks	azi 500 mg qd x 3 days clari 250 mg bid x 10 days	Not described	Outcomes:

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Adler, 2000 USA, Canada	At entry, sputum collected for GS, cx Repeat cx at 2 f/u visits Outcomes: presumed erad: in absence of repeat sputum cx, definiton of clinical cure met erad: study entry pathogen(s) absent from repeat cx at day 19-21 visit presumed persistence: in absence of repeat sputum cx, definition of clinical failure met persistence: original pathogen(s) present in repeat cx at day 19-21 visit or at D/C of tx superinfxn: new pathogen(s) present in cx at day 8-10 or 19-21 visits in a symptomatic pt indeterminate: assessment not possible	Mean age (yr): ER 54.3, IR 54.6 Gender (M/F): ER 136/181, IR 134/169 Ethnicity: white, black, asian, "other"	No sig differences in weight, tobacco use, pre-tx signs, sx of AECB, isolated pathogens Sig difference in # AECB episodes in prior 12 months: ER 2.9, IR 3.2 (P=0.048) Sig difference in # w/ mod to severe sputum production: ER 81%, IR 86% (P=0.042)	screened not reported eligible not reported 627 enrolled	6 lost to f/u 1 D/C'd due to criteria violation excluded from ITT: 35 excluded due to not meeting selection criteria or protocol violation excluded from clinically evaluable: 65 excluded due to protocol violations, missing ≥ 1 visit, use of confounding med premature D/C: 7% each group ITT analyzed: 585 clinically evaluable analyzed: 520 clinically + bacteriologically evaluable analyzed: 182
Bradbury, 1993 Ireland, Germany	Eval: blood, sputum cx at day 10-14 Outcomes: erad: not isolated on f/u or no sputum to test colonization: organisms not considered pathogens isolated erad/re-infxn: baseline pathogen eradicated then reappeared superinfection: no pathogen isolated	Mean age (yr): azi 52.2, clari 53.9 (entire study) Gender (M/F): azi 148/104, clari 152/106 Ethnicity not reported By dx: AIECB 75 vs 68	No sig differences in disease severity or frequency or smoking	screened not reported eligible not reported 510 in entire study population 143 enrolled w/ AIECB	w/d: 22 lost to f/u not reported 488 analyzed (entire study) eval for AIECB: 138

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Adler, 2000 USA, Canada	Evaluable, day 19-21 visit: clinical cure: ER 83/100 (83%), IR 67/82 (82%) At TOC visit, no sig differences in sx resolution, except resolution of purulent sputum (ER 96%, IR 85%; P=0.028) ITT results not reported; "similar" to results for evaluable pts	Evaluable, day 19-21 visit: bacteriologic cure: ER 85/99 (86%), IR 70/82 (85%) pathogen eradication: ER 100/116 (86%), IR 86/98 (88%) ITT results not reported; "similar" to results for evaluable pts	Monitored by investigators: PE, labs (chemistry, hematology); pts directed to contact investigator in case of ADR Causality and severity assessed by investigators Compliance assessed by pill counts	Total ADR: ER 70/317 (22%), IR 52/203 (17%) serious ADR: 8 ER, 4 IR (all but 1 ER [atrial flutter] considered unrelated to study med) diarrhea: ER 6%, IR 4% altered taste: ER 4%, IR 4% nausea: ER 3%, IR 3% D/C due to ADR: 9 ER, 9 IR (3 ER, 6 IR due to GI ADR) No clinically meaningful changes in labs noted Compliance (took ≥ 80% med): ER 100%, IR 95% (P=0.009)	w/d due to ADR: 9 ER, 9 IR
Bradbury, 1993 Ireland, Germany	AIECB, day 10-14: cure: azi 68%, clari 64% improved: azi 27%, clari 33% failure: azi 5%, clari 3%	Day 10-14, AIECB only: erad: azi 25/25 (100%), clari 27/29 (93.1%)	Pt reports	Entire study, all ADR: azi 22/252 (9%), clari 16/258 (6%) GI: azi 15/252, clari 10/258 abd pain: azi 1/252, clari 3/258 diarrhea: azi 9/252, clari 2/258 nausea: azi 1/252, clari 1/258	1 azi, 3 clari w/d due to ADR

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Adler, 2000 USA, Canada	Note that microbiologic responses reported by organism (date not included here)
Bradbury, 1993 Ireland, Germany	Multiple conditions study Note: needed to take 50% med to be eligible for analysis; only 1 pt excluded for this

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Castaldo, 2003 USA	Single-blind (investigator-blind), randomized, parallel-group Multicenter	Age > 35 yr Acute exac judged likely to have bacterial cause (exac required to include worsening dyspnea and/or increase in amount or viscosity of phlegm or a change in its color, and fever w/in 48h enrollment) Exclusion: hx macrolide hypersens, clinical or radiographically demonstrated dx pneumonia, known malignancy or cardiopulmonary d/o, known HIV infxn, other long-standing causes of immunosuppression, use of ABX or investigational med w/in 30 days	azi 500 mg x1, 250 mg qd x 4 days dir 500 mg qd x 5 days	Not described	Visit 1 = enrollment (day 0), visit 2 = days 7-10 (early post-tx), visit 3 = days 25-35 (late post-tx) ITT: all pts who received ≥ 1 dose study med, had ≥ 1 post-tx eval Clinical assessment and PE at all visits; standard AECB assessment included recording of heart rate, BP, RR, temp, presence/absence of specific cardipulmonary findings; pts questioned about changes in sx of cough, phlegm, dyspnea, overall status (also assessed by investigator) Labs at visit 1 = CBC, WBC, biochem; at visit 2 = WBC Clinical outcomes: success (overall sx improved or resolved) failure (overall sx the same or worse)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Castaldo, 2003 USA	Sputum sample obtained before enrollment (but not required for entry) and at visit 2 Microbiologic cure not systematically reported	Mean age (yr): azi 54.9, dir 56 Gender (M/F): azi 19/21, dir 19/27 Ethnicity: white, black, hispanic	No sig differences in smoking, coexisting medical conditions, duration and severity of current AECB, signs and sx of CB, PE findings, WBC, single organism in sptum Gram stain	screened not reported eligible not reported 86 enrolled 86 in study population	3 azi, 3 dir excluded from per-protocol analysis (2 denied fever in the 2 days before entry, 1 aged < 35 yr, 1 reported no change in phlegm or increased dyspnea in current AECB, 2 did not complete study med) 83 analyzed (3 missing in azi analysis for unknown reason)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Castaldo, 2003 USA	Overall, day 7-10: (n=83) success: azi 25/37 (67.6%), dir 39/46 (84.8%) Overall, day 30 versus day 0: (n=83) success: azi 32/37 (86.5%), dir 41/44 (93.2%) Additional ABX required at visit 2 or 3: azi 10/37 (27%), dir 9/44 (20.5%) No sig difference in change in WBC	Not reported	ADR recorded after visit 1; included worsening of respiratory sx, new nonrespiratory sx, any medical or clinical abnormality	1 or more ADR reported: azi 17/40 (42.5%), dir 15/46 (32.6%) ADR reported by ≥ 2 pts: worsening bronchitis sx: azi 7/40 (17.5%), dir 6/46 (13%) sinusitis: azi 3/40 (7.5%), dir 1/46 (2.2%) back pain: azi 2/40 (5%), dir 1/46 (2.2%) pain: azi 0/40 (0%), dir 2/46 (4.3%)	0 w/d due to ADR

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Castaldo, 2003 USA	Note that 3 pts not included for azi in efficacy analysis; these 3 pts not described Clinical responses divided by pt reported and physician assessed; only physician assessed reported here (results also reported specifically for pts w/ neutrophil-predominant sputum; these results also not reported here)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Cazzola, 1999 Not reported	Randomized, single-blind, parallel-group	Age not specified AECB: alteration in quiescent state of pt w/ CB, w/ increase in cough frequency, increase in sputum quantity and/or purulence, presence of pulm crackles or rhonchi, isolation of pathogen Exclusion: macrolide hypersens, ABX w/in 1 week entry, sig renal or hepatic impairment, hematologic abnormalities, underlying medical d/o that would interfere w/ eval, active TB, CF, lung carcinoma, HIV	azi 500 mg qd x 3 days dir 500 mg qd x 5 days	Not described	Eval at baseline (visit 1), day 10 +/- 2 (post-tx visit), day 28 +/- 4 (late post-tx); cough, sputum production, sputum quality, dyspnea, fever assessed according to 4-point scale Outcomes: cure: elimination signs, sx w/ no recurrence at late post-tx visit improvement: marked or mod reduction in severity and/or #'s of signs, sx w/ no further ABX required relapse: reappearance of signs, sx up to 28 +/- 4 days post-tx after initial cure failure: no improvement signs, sx
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	Randomized, non-blinded (except to cx results, which were blinded) Multicenter	Age >18 yr acute bacterial infxn, including acute infectious exac CB, pneumonia (no further defintions of infxn added) Exclusion: chronic pulm dx w/o acute infective exac, life-threatening conditions, cystic fibrosis, receipt of ABX w/in 48h, any factor affect6ing drug absorption, drug or alcohol abuse, tx w/ warfarin, carbamazepine, or ergotamine CXR not required or mentioned	azi 500 mg x 1, then 250 mg qd on days 2-5 ery (stearate salt) 500 mg qid x 7-10 days (7-day target w/ option to extend to 10 days if deemed "appropriate")	Not described	Clinical response determined at visit 4 (TOC)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Cazzola, 1999 Not reported	Outcomes: erad: elimination of baseline pathogen persistence: failure of erad of baseline pathogen recurrence: erad during tx, w/ presence of infecting organism at last visit reinfxn: clearance of original pathogen but isolation of new pathogen unevaluable: erad of causal pathogen implied by absence of appropriate material for cx or cx not indicated indeterminate: bacteriologic response not defined	Mean age (yr): azi 58.9, dir 57.6 Gender (M/F): azi 29/11, dir 32/8 Ethnicity not reported	No sig differences in weight	screened not reported eligible not reported 80 enrolled	3 azi, 4 dir missing from late post-tx visit (reasons not described)
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	Eval at day 10-15 Outcomes: erad: organism not cx'd again, or lack of sputum production	Age not reported Gender (M/F): 93/88 (entire study) Ethnicity: 84/88 white	All bronchitis: azi 77%, ery 75% (AIECB not differentiated)	screened not reported eligible not reported 181 in total study population 138 all bronchitis (# AIECB not individually stated)	w/d N/A lost to f/u N/A analyzed not reported

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Clinical cure**	**Microbiological cure**	**Method of adverse effects assessment**	**Adverse effects reported**	**Total withdrawals; withdrawals due to adverse events**
Cazzola, 1999 Not reported	post-tx visit: cure + improvement: azi 37/40 (92.5%), dir 36/40 (90%) failure: azi 3/40 (7.5%), dir 4/40 (10%) late post-tx visit: cure + improvement: azi 33/37 (89.2%), dir 34/36 (94.4%) failure: azi 4/37 (10.8%), dir 2/36 (5.6%) No sig differences in any clinical signs, sx	post-tx visit: erad: azi 37/40 (92.5%), dir 36/40 (90%) late post-tx visit: erad: azi 33/37 (89.2%), dir 34/36 (94.4%) persistence of *H. flu* in 2/9 (22.2%) azi, 3/11 (27.3%) dir	Pt reporting Severity assessment: mild, mod, severe Causality assessed by investigators	Total ADR: azi 5/40 (12.5%), dir 4/40 (10%) nausea: azi 3/40 (7.5%), dir 2/40 (5%) abd cramps: azi 1/40 (2.5%), dir 1/40 (2.5%) diarrhea: azi 1/40 (2.5%), dir 1/40 (2.5%)	3 azi, 4 dir missing from late post-tx visit (reasons not described) 0 w/d due to ADR described
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	AIECB: azi 64%, ery 74%	Entire study, including bronchitis of all types: erad: azi 80%, ery 86%	Voluntary pt reporting	Entire study, all ADR: azi 5/93 (5%), ery 16/88 (18%)	1 ery w/d due to ADR

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Cazzola, 1999 Not reported	None
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	Multiple conditions study Note: poor study - incomplete diagnostics, and no differentiation of # pts w/ each dx

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Gotfried, 2005 "North America"	Randomized, double-blind, parallel-group, comparative Multicenter	Age > 40 yr ABECB: presumptive dx made w/in 14 days entry; based on presence of at least 2 of increased dyspnea, increased sputum volume, or increased sputum purulence; pre-tx purulent sputum sample obtained w/in 48h entry required for dx Exclusion: severe or complicated RTI (including pneumonia), any resp condition that would confound eval (tumor, bronchiectasis, etc), sig renal or hepatic impairment, immunocompromised or oxygen-dependent pts, use of systemic ABX w/in 1 week (2 weeks for azi, 4 weeks for long-acting ABX) entry or concomitantly	clari ER 1000 mg qd + placebo of IR x 5 days clari IR 500 mg bid + placebo of ER x 7 days	Not described	Eval at baseline (visit 1), day 3-4 (visit 2), day 8-10 (visit 3, EOT), day 17-21 (visit 4, TOC), day 37-40 (visit 5) Clinical response determined at visit 4 (TOC) Outcomes: cure: resolution of dyspnea, sputum volume, sputum purulence to pre-acute levels or resolution of at least 2 of the former w/ improvement in at least half of remaining signs, sx failure: continuation or worsening of signs, sx w/ further ABX neeed indeterminate: eval not possible

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Gotfried, 2005 "North America"	Determined at visit 4 (TOC) Outcomes: erad: pathogen isolated from pre-tx sputum cx absent from repeat sputum cx presumed erad: no repeat sputum cx available and clinical cure occurred persistence: pathogen isolated from pre-tx sputum cx isolated from sputum cx at visit 4 or study D/C presumed persistence: no repeat sputum cx available and pt classified as failure superinfxn: isolation of new pathogen(s) during tx in symptomatic pt indeterminate: eval not possible new infxn: isolation of new pathogen from post-tx cx in a symptomatic pt colonization: isolation of new pathogen from post-tx cx in an asymptomatic pt recurrence: isolation of original pathogen(s) from cx taken after visit 4 in a symptomatic pt	Mean age (yr): ER 62.1, IR 61.6 Gender (M/F): ER 117/123, IR 118/127 Ethnicity: white, black, "other"	No sig differences in medical hx, social hx, clinical presentation, tobacco use, pathogen suscept	screened not reported eligible not reported 485 enrolled	excluded from ITT: 41 (30 selection criteria not met, 9 D/C'd by investigator, 2 w/ no confirmation of dx) excluded from clinically evaluable: 94 ITT analyzed: 444 clinically evaluable analyzed: 391

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Gotfried, 2005 "North America"	Per-protocol, TOC visit: cure: ER 157/187 (84%), IR 172/204 (84%) ITT, TOC visit: cure: 158/218 (72%), IR 172/226 (76%)	Per-protocol, TOC visit: bacteriologic cure: ER 82/94 (87%), IR 91/102 (89%) overall erad: ER 107/122 (88%), IR 117/131 (89%) ITT, TOC visit: bacteriologic cure: 82/105 (78%), IR 91/111 (82%)	ADR monitored across study visits by lab tests (chemistry, hematology), medical history, PE, VS, occurrence of ADR, use of concomitant meds Severity assessment: mild, mod, severe Causality assessment: probably, possibly, probably not, or not related to study med Compliance assessed by pill counts	Total ADR: ER 31/240 (13%), IR 45/245 (18%) GI ADR: ER 19/240 (8%), 26/245 (11%) abd pain: ER 8/240 (3.3%), IR 14/245 (5.7%) nausea: ER 9/240 (3.8%), IR 10/245 (4.1%) vomiting: ER 2/240 (< 1%), IR 5/245 (2%) abnormal taste: ER 6/240 (2.5%), IR 19/245 (7.8%) [P<0.05] D/C due to ADR: 6 (3%) ER, 4 (2%) IR (most due to GI ADR) serious ADR: 0 ER, 1 IR w/ myopathy No clinically meaningful changes in labs noted Compliance (rate): ER 96.5%, IR 97.2%	D/C due to ADR: 6 (3%) ER, 4 (2%) IR (most due to GI ADR)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Gotfried, 2005 "North America"	Note that microbiologic responses reported by organism (date not included here) No sig differences in clinical response when adjustments made for country, gender, race, age, weight, study med duration, tobacco and alcohol use, FEV)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Hosie, 1995 UK, Ireland	Randomized, single-blind, parallel-group Multicenter	Age ≥ 18 yr AECB: increase in volume and change in purulence of sputum w/ increased dyspnea Exclusion: any condition thought to preclude satisfactory eval, anticipated need for alternate ABX, use of ABX w/in 3 days entry, use of investigational med w/in 1 mo entry, CXR evidence of pneumonia w/in 24h entry, macrolide hypersens	clari 250 mg bid x 7 days dir 500 mg qd x 5 days	Concomitant non-ABX permitted	Eval at day 0, day 3-4 (during tx), day 10-12 (post-tx), day 20-30 (late post-tx) Pts examined and/or questioned at each visit for presence and severity of AECB-related sx (cough, pruductive sputum, dyspnea, wheezing, chest pain, rigors, tachypnea, rhonchi, rales) Outcomes: cure: elimination of signs, sx w/ no recurrence improvement: sig but incomplete resoluton signs, sx relapse: worsening of signs, sx following initial improvement failure: no improvement of signs, sx indeterminate: inability to eval response
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	Randomized, double-blind, double-dummy, parallel-group, comparative Multicenter	Age 40-75 yr ABECB: presumptive dx made w/in 14 days entry; based on standardized Anthonisen criteria (including increased dyspnea, increased sputum volume and purulence, productive cough w/ purulent sputum at entry) Exclusion: severe or complicated RTI, severely compromised resp status, immunocompromised pts, sig renal or hepatic disease, use of systemic ABX w/in 2 weeks entry or concomitantly	clari ER 500 mg qd + placebo of IR x 5 days clari IR 250 mg bid + placebo of ER x 5 days	Not described	Eval at baseline (visit 1), day 3 (visit 2), day 8-25 (visit 3 - TOC), day 40-50 (visit 4 - f/u) Outcomes at TOC and f/u visits: cure: resolution signs, sx or improvement to baseline level w/o additional ABX failure: continuation or worsening of baseline signs, sx w/ further ABX needed indeterminate: eval not possible

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Hosie, 1995 UK, Ireland	At entry, sputum collected for GS, cx Subsequent eval at all f/u visits if indicated Outcomes (f/u cx obtained): erad: original pathogen eliminated persistence: continued presence of original pathogen relapse: suppression w/ recurrence of original pathogen colonization: presence of organism other than original pathogen in absence of signs, sx of infxn superinfxn: emergence of new pathogen during tx w/ signs, sx of infxn erad w/ reinfxn: erad of original pathogen w/ infxn by new pathogen after completion of tx Outcomes (no f/u cx obtained): erad: implied by absence of material for cx or no clinical indication for cx indeterminate: pathogen not obtained before tx or response could not be defined	Mean age (yr): clari 61.1, dir 62.7 Gender (M/F): clari 63/45, dir 60/44 Ethnicity not reported	No sig differences in underlying resp pathology, smoking, weight, receipt of other medical therapy	screened not reported eligible not reported 212 enrolled	clinically unevaluable: lack initial cx: 6 loss to f/u: 5 unevaluability by investigator: 4 concomitant med: 3 insufficient tx: 2 underlying condition: 2 ITT analyzed: 212 evaluable analyzed: 191
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	Determined at visit 3 (TOC) Outcomes: erad: pathogen isolated from pre-tx sputum cx absent from repeat sputum cx presumed erad: no repeat sputum cx available and clinical cure occurred persistence: pathogen isolated from pre-tx sputum cx isolated from sputum cx at visit 3 or study D/C presumed persistence: no repeat sputum cx available and pt classified as failure superinfxn: isolation of new pathogen(s) during tx in symptomatic pt	Mean age (yr): ER 58.1, IR 57.4 Gender (M/F): ER 218/133, IR 207/145 Ethnicity (% white): ER 99%, IR 99%	No sig differences in pre-tx signs, sx, presenting conditions, medical and social hx	screened not reported eligible not reported 703 enrolled	excluded from ITT: 0 excluded from clinically evaluable: 89 (44 ER, 45 IR)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Hosie, 1995 UK, Ireland	ITT, post-tx: cure or improvement: clari 100/108 (92.6%), dir 90/104 (86.5%) relapse: clari 1/108 (0.9%), dir 0/104 (0%) failure: clari 4/108 (3.7%), dir 10/104 (9.6%) ITT, late post-tx: cure or improvement: clari 86/108 (95.5%), dir 87/104 (98.8%) relapse: clari 4/108 (4.4%), dir 1/104 (1.1%) Evaluable, post-tx: cure or improvement: clari 91/96 (94.8%), dir 85/95 (89.5%) relapse: clari 1/96 (1%), dir 0/95 (0%) failure: clari 4/96 (4.2%), dir 10/95 (10.5%) Evaluable, late post-tx: cure or improvement: clari 81/96 (95.3%), dir 82/95 (98.8%) relapse: clari 4/96 (4.7%), dir 1/95 (1.2%)	Overall erad (pts w/ pre-tx positive cx): clari 23/32 (71.9%), dir 22/32 (68.8%)	Recorded in pt's own words Compliance assessed by pill counts	Total ADR: pts w/ an ADR: clari 17/108 (15.7%), dir 13/104 (12.5%) most frequent ADR = GI (clari 7.4%, dir 5.8%; specific #'s not reported) Compliance (failure to complete tx): clari 12, dir 4	7 w/d due to ADR (5 clari, 2 dir)
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	ITT TOC: cure: ER 309/351 (88%), IR 311/352 (88%) ITT f/u: cure: ER 316/351 (90%), IR 321/352 (91%) per-protocol TOC: cure: ER 298/307 (97%), IR 300/307 (98%) per-protocol f/u: cure: ER 280/301 (93%), IR 287/301 (95%)	ITT TOC: cure (% w/ erad): ER 139/176 (79%), IR 140/180 (78%) erad: ER 172/191 (90%), IR 175/194 (90%) per-protocol TOC: cure (% w/ erad): ER 134/150 (89%), IR 136/153 (89%)	Eval throughout study by periodic lab tests, PE, ADR monitoring Severity assessment: mild, mod, severe Causality assessment: probably, possibly, probably not, or not tx-related	Total ADR: ER 23/351 (7%), IR 19/352 (5%) abd pain: ER 1%, IR 1% diarrhea: ER 2%, IR 1% taste perversion: ER 1%, IR 1% D/C due to ADR: 1 ER, 1 IR serious ADR: 7 ER, 3 IR (all considered tx-unrelated) No clinically meaningful changes in labs noted Compliance (rate): ER >99%, IR > 99%	1 ER, 1 IR w/d due to ADR

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Hosie, 1995 UK, Ireland	Note that microbiologic responses reported by organism (date not included here)
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	Note that microbiologic responses reported by organism (date not included here)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Sides, 1993 USA?	Double-blind, randomized, parallel	Age not specified ABECB: cough, purulent sputum, and CXR free from acute pulm infiltrates Exclusion: hx renal impairment (serum creatinine ≥ 133 µmol/L), macrolide hypersens, use of ABX w/in 1 week entry, previous participation in an investigational study w/in 21 days entry	ery 250 mg qid x minimum 7 days dir 500 mg qd x minimum 7 days placebo given to dir pts to maintain blinding	Any necessary for tx of underlying diseases or conditions, other than systemic ABX	Before entry, hx and PE and sputum obtained for GS, cx, susceptibility testing ITT: all pts "qualified pt analysis": all pts enrolled who received at least 5 days study med, had positive pre-tx sputum cx, returned for post-tx eval, had evaluable symptomatic response Assessments on days 3-5, w/in 3-5 days after EOT (post-tx), w/in 10-12 days after EOT (late post-tx) Clinical outcomes: cure improvement relapse failure unable to eval
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	Randomized, double-blind, comparative Multicenter	Age 35-75 yr ABECB: dx based on increased cough or sputum production, worsening dyspnea, purulent sputum; pre-tx sputum GS must have demonstrated purulence Exclusion: CXR dx of pneumonia, macrolide hypersens, use of systemic ABX w/in 7 days entry, any clinically sig diseases or lab abnormalities, any condition that may preclude eval, hepatic impairment, additional infxn requiring another ABX, use of investigational med w/in 4 weeks entry, prior enrollment in this trial	azi 500 mg qd x 3 days clari 500 mg bid x 10 days	Not described	Eval at day 10-12 (EOT), day 21-24 (TOC); primary endpoint = response at TOC Outcomes at EOT: cure: resolution signs, sx (including cough, purulent sputum production, character of sputum, dyspnea) to pre-ABECB level improvement: partial resolution signs, sx failure: lack of resolution signs, sx or use of additional ABX due to inadequate response success: cure + improvement At TOC, assessment of cure or failure made; if improvement at TOC, assessment of cure or failure made at f/u visit in 1-2 weeks

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed
Sides, 1993 USA?	Not described; sputum cx at each visit "if appropriate", and at entry pt had to have sputum cx positive for respiratory pathogen Outcomes: erad presumed erad (no f/u specimen obtainable)	Mean age (yr): ery 54.6, dir 52.4 Gender (M/F): ery 183/226, dir 179/214 Ethnicity: caucasian, black, hispanic, native American, asian	No sig differences in height, weight	screened not reported eligible not reported 802 enrolled 641 in study population ery: of 409 enrolled, 320 completed protocol, 81 qualified for post-therapy eval, 67 qualified for late post-therapy eval dir: of 393 enrolled, 321 completed protocol, 101 qualified for post-therapy eval, 80 qualified for late post-therapy eval	ery: 89 did not complete protocol, 239 did not qualify for post-therapy eval, 253 did not qualify for late post-therapy eval dir: 72 did not complete protocol, 220 did not qualify for post-therapy eval, 241 did not qualify for late post-therapy eval 14 lost to f/u ITT analyzed: 802 evaluable analyzed: 182
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	Outcomes: erad: elimination of baseline pathogen presumed erad: pt clinically cured or improved in absence of adequate sputum for cx persistence: failure to eradicate baseline pathogen presumed persistence: clinical outcome = failure in absence of adequate sputum for cx superinfxn: baseline pathogen(s) not recx'd but another pathogen isolated not available: no sputum cx and outcome was not failure success = erad or presumed erad	Mean age (yr): azi 61.4, clari 57.9 Gender not reported by group Ethnicity: caucasian, negroid, asian, "other"	No sig differences in tobacco use, prior duration and severity of signs, sx, PMH, concomitant med use prior to entry, pulm function values	screened not reported eligible not reported 322 enrolled	excluded from MITT: 4 (did not meet inclusion criteria) MITT analyzed: 318 per-protocol EOT analyzed: 288 per-protocol TOC analyzed: 285

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Sides, 1993 USA?	ITT post-tx: cure or improvement: ery 331/409 (80.9%), dir 306/393 (77.9%) ITT late post-tx: cure or improvement: ery 144/155 (92.9%), dir 139/157 (88.5%) Evaluable post-tx: cure or improvement: ery 72/81 (89%), dir 87/101 (86%) Evaluable late post-tx: cure or improvement: ery 60/67 (89.6%), dir 70/80 (87.5%)	ITT post-therapy: erad or presumed erad: ery 122/409 (29.8%), dir 136/393 (34.6%) ITT late post-therapy: erad or presumed erad: ery 75/154 (48.7%), dir 89/155 (57.4%) Evaluable post-therapy: erad or presumed erad: ery 66/81 (82%), dir 85/101 (84%) erad or presumed erad: ery 60/67 (89.6%), dir 70/80 (87.5%)	Pts asked to contact investigators in case of any ADR; all recorded, including events occurring for 1st time and worsening of pre-existing ADR	D/C due to ADR: ery 21, dir 20 (11 ery, 10 dir due to GI ADR; remaining not thought tx-related) abd pain: ery 31/409 (7.6%), dir 32/393 (8.1%) nausea: ery 24/409 (5.9%), dir 30/393 (7.6%) diarrhea: ery 38/409 (9.3%), dir 16/393 (4.1%) (P=0.043) vomiting: ery 9/409 (2.2%), dir 12/393 (3.1%) No sig differences in lab test results (hemat, biochem, urinalysis)	ery: 89 did not complete protocol, 239 did not qualify for post-therapy eval, 253 did not qualify for late post-therapy eval dir: 72 did not complete protocol, 220 did not qualify for post-therapy eval, 241 did not qualify for late post-therapy eval w/d due to ADR: ery 21/409 (5.1%), dir 20/393 (5.1%)
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	MITT EOT: cure: azi 77/155 (%), clari 77/163 (%) improvement: azi 61/155 (%), clari 74/163 (%) success: azi 138/155 (93%), clari 151/163 (94%) failure: azi 11/155 (7%), clari 9/163 (6%) MITT TOC: cure: azi 127/149 (85%), clari 129/157 (82%) failure: azi 22/149 (15%), clari 28/157 (18%)	MITT EOT: erad: azi 10/56 (17.9%), clari 11/60 (18.3%) presumed erad: azi 42/56 (75%), clari 44/60 (73.3%) success: azi 52/56 (92.9%), clari 55/60 (91.7%) MITT TOC: erad: azi 9/56 (16.1%), clari 5/56 (8.9%) presumed erad: azi 39/56 (69.6%), clari 40/56 (71.4%) success: azi 48/56 (85.7%), clari 45/56 (80.4%)	ADR (either reported by pt or observed by investigator) recorded at each visit Severity assessment: mild, mod, severe Causality assessed by investigator	Total ADR: azi 33/158 (20.9%), clari 44/164 (26.8%) abd pain: azi 10/158 (6.3%), clari 10/164 (6.1%) diarrhea: azi 7/158 (4.4%), clari 9/164 (5.5%) nausea: azi 7/158 (4.4%), clari 6/164 (3.7%) taste perversion: azi 1/158 (0.6%), clari 13/164 (7.9%) D/C due to ADR: azi 0, clari 5 (causes not listed) serious ADR: 0 azi, 0 clari	0 azi, 5 clari w/d due to ADR (reasons not described)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Sides, 1993 USA?	Note that clinical responses also differentiated by bug (data not included here)
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	Note that microbiologic responses reported by organism (date not included here)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Wasilewski, 1999 "North America"	Randomized, well-controlled, double-blind	Age ≥ 12 yr AECB: sig increase in sputum production and in frequency and severity of cough, w/ 2 or more of following diagnostic findings: fever, cough, dyspnea, rhonchi, coarse rales; microbiologic evidence of infxn and pre-tx sputum w/ ≥ 25 WBC required Exclusion: any condition precluding eval of response, known or anticipated requirement for systemic ABX, macrolide hypersens, use of systemic ABX w/in 7 days entry, participation in a prior dir trial, participation in trial involving investigational med w/in 30 days entry, pts w/ pneumonia (dx'd by CXR)	ery 250 mg qid x 7 days dir 500 mg qd x 5 days placebo given to ery + dir pts to maintain blinding	Any concomitant med for tx of underlying diseases, except systemic ABX	Eval at day 3-5 (post-tx), day 10-14 (late post-tx) Clinically evaluable if pt met inclusion criteria and all data collected Outcomes: cure: elimination of signs, sx w/ no recurrence at f/u visits improvement: sig, but incomplete resolution of signs, sx relapse: worsening of signs, sx following initial improvement failure: no improvement unappraisable: pt could not be assigned to a category (D/C'd from analysis)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Wasilewski, 1999 "North America"	Eval at day 3-5 (post-tx), day 10-14 (late post-tx) Microbiologic eval if pre-tx sputum cx positive for respiratory pathogen (*H. flu* , *Kleb. pneumo* , *S. pneumo* , *Kleb. spp* , *M. cat* , *S. aureus* , *H. paraflu* , group A strep Outcomes (f/u cx obtained): erad: pathogen eliminated persistence: cx positive for original pathogen relapse: recurrence of same pathogen w/ or w/o development resist colonization: cx positive for new pathogen w/o signs of infxn superinfxn: cx positive for new pathogen during tx, w/ clinical failure or relapse erad w/ reinfxn: cx positive for new pathogen after tx, w/ clinical failure or relapse Outcomes (f/u cx not obtained): presumed erad: absence of appropriate cx material or no clinical indication for cx, w/ clinical cure or improvement presumed persistence: clinical relapse or failure indeterminate: could not be eval'd, or no pre-tx cx	Mean age (yr): ery 52, dir 52 Gender (M/F): ery 275/251, dir 286/245 Ethnicity: asian, black, caucasian, hispanic, native American, "other" Note that demographics reported for combined 2 studies	None described	screened not reported eligible not reported 1057 enrolled (total in both studies) 499 enrolled in study 1 558 enrolled in study 2	ery, clinically unevaluable: entry criteria violation: 151 protocol violation: 121 unevaluable by investigator: 3 > 1 reason: 128 dir, clinically unevaluable: entry criteria violation: 144 protocol violation: 83 unevaluable by investigator: 3 > 1 reason: 177 lost to f/u not reported Study 1: ITT 499 clinically evaluable 323 Study 2: ITT 558 clinically evaluable 367

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Wasilewski, 1999 "North America"	All responses are "favorable response" (cure or improvement) ITT, post-tx: study 1: ery 208/250 (83.2%), dir 206/249 (82.7%) study 2: ery 206/276 (74.6%), dir 219/282 (77.7%) total: ery 414/526 (78.7%), dir 425/531 (80%) ITT, at termination: study 1: ery 194/250 (77.6%), dir 197/249 (79.1%) study 2: ery 182/276 (65.9%), dir 196/282 (69.5%) total: ery 376/526 (71.5%), dir 393/531 (74%) Evaluable, post-tx: study 1: ery 137/159 (86.2%), dir 133/164 (81.1%) study 2: ery 133/177 (75.1%), dir 165/190 (86.8%) total: ery 270/336 (80.4%), dir 298/354 (84.2%) Evaluable, at termination: study 1: ery 127/159 (79.9%), dir 127/164 (77.4%) study 2: ery 116/177 (65.5%), dir 146/190 (76.8%) total: ery 243/336 (72.3%), dir 273/354 (77.1%)	All responses are "favorable response" (erad or presumed erad) ITT, post-tx: study 1: ery 141/250 (56.4%), dir 122/249 (49%) study 2: ery 114/276 (41.3%), dir 132/282 (46.8%) total: ery 255/526 (48.5%), dir 254/531 (47.8%) ITT, at termination: study 1: ery 135/250 (54%), dir 121/249 (48.6%) study 2: ery 103/276 (37.3%), dir 125/282 (44.3%) total: ery 238/526 (45.2%), dir 246/531 (46.3%) Evaluable, post-tx: study 1: ery 88/108 (81.5%), dir 76/103 (73.8%) study 2: ery 82/108 (75.9%), dir 102/125 (81.6%) total: ery 170/216 (78.7%), dir 178/228 (78.1%) Evaluable, at termination: study 1: ery 86/108 (79.6%), dir 76/103 (73.8%) study 2: ery 74/108 (68.5%), dir 95/125 (76%) total: ery 160/216 (74.1%), dir 171/228 (75%)	All ADR recorded; determined at each visit by questioning pt (occurrence and nature of ADR); pts also instructed to contact investigators in case of ADR; unspecified lab test eval Compliance assessed by pill counts	Total ADR (both studies): pts w/ at least 1 event: ery 233/526 (44.3%), dir 267/531 (49.7%) nausea: ery 41/526 (7.8%), dir 36/531 (6.8%) diarrhea: ery 50/526 (9.5%), dir 35/531 (6.6%) abd pain: ery 32/526 (6.1%), dir 31/531 (5.8%) Compliance: ery 438/504 (86.9%), dir 488/499 (97.8%) (P<0.001)	0 w/d due to ADR

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Comments**
Wasilewski, 1999 "North America"	Report of 2 trials Note that microbiologic responses reported by organism (date not included here)

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Study design Setting**	**Eligibility criteria**	**Interventions**	**Allowed other medications/ interventions**	**Method of outcome assessment and timing of assessment - Clinical cure**
Weiss, 2002 Canada	Randomized, open-label, comparative, phase 3 Multicenter	Age ≥ 18 yr Productive cough, purulent sputum w/ minimum 2 other sx indicative of type 2 AECB: worsening dyspnea, increased sputum production, and increased sputum purulence; fever w/o other cause; increased wheezing; increased coughing Positive cx for study pathogen (*M. cat* , *H. flu* , *S. pneumo*) not required Exclusion: CXR evidence of pneumonia, active TB, lung tumor, use of systemic ABX w/in 14 days (4 weeks if long-acting), any other acute infxn, hx macrolide hypersens, hx CF or bronchiectasis, uncontrolled illness expected to influence clinical course, use of investigational med w/in 4 weeks, prior tx in this study, known sig hepatic or renal disease	clari ER 500 mg qd x 7 days clari IR 250 mg bid x 7 days	Not described	Visit 1 = pre-tx visit w/in 48h entry (medical hx, PE, VS, blood samples (hemat, biochem), CXR, clinical signs, sx of infxn (cough, sputum production and apperance, dyspnea, rales/crackling, rhonchi/wheezing, chest tightness, pleuritic pain and effusion, egophony, fever, coryza, hoarseness, sore throat, fatigue), sputum (obtained for GS, cx) Pt w/o sputum cx w/ target pathogen included in clinical analysis, but not bacteriologic analysis Visit 2: clinical response assessed w/in 48h after EOT Visit 3: TOC visit 21 ± 2 days post-EOT Clinical outcomes: cure: pre-tx signs, sx resolved or returned to pre-infxn baseline w/o need for additional ABX improvement: pre-tx signs, sx improved but did not resolve failure (visit 2 only): pre-tx signs, sx did not improve or worsened above baseline level or at the time of D/C of study med, warranting further ABX indeterminate: could not be detemined (e.g., pt took < 3 days study med or no f/u performed) relapse (visit 3 only): signs, sx worsened or reappeared w/in 21-day post-tx f/u

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**	**Number screened/ eligible/ enrolled**	**Number withdrawn/ lost to fu/analyzed**
Weiss, 2002 Canada	Pt w/o sputum cx w/ target pathogen included in clinical analysis, but not bacteriologic analysis Visit 2: bacteriologic response assessed w/in 48h after EOT Visit 3: bacteriologic response at test-of-cure visit 21 ± 2 days post-EOT Outcomes: presumed erad: in absence of repeat sputum cx, clinical cure determined erad: entry pathogen absent from repeat sputum cx performed at visits 2, 3 presumed persistence: in absence of repeat sputum cx, clinical failure determined persistence: entry pathogen present in repeat sputum cx performed at visits 2, 3 or time of D/C superinfxn: presence of new pathogen in a visit 2 or 3 sputum cx from a symptomatic pt indeterminate: pt did not qualify for efficacy analysis	Mean age (yr): ER 59.9, IR 59.6 Age range (yr): ER 24-87, IR 24-85 Gender (M/F): ER 57/61, IR 48/67 Ethnicity (% white): ER 97.5%, IR 95.7% (other ethnicity reported: "other")	No sig differences in % > 60 yr, % w/ CHF dx, smoking, medical hx, concomitant meds, signs, sx of AECB	screened not reported eligible not reported 233 enrolled	completed protocol: ER 84/115 (73%), IR 78/115 (67.8%) safety-evaluable population: 68/233 total (29.2%) D/C'd w/d due to failure: ER 14/117 (12%), IR 9/113 (8%) 5 ER, 5 IR D/C'd due to protocol violation lost to f/u: not reported 162 analyzed at TOC visit 3

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year Country Trial Name	Clinical cure	Microbiological cure	Method of adverse effects assessment	Adverse effects reported	Total withdrawals; withdrawals due to adverse events
Weiss, 2002 Canada	ITT TOC: cure: ER 72/88 (81.8%), IR 68/83 (81.9%) improvement: ER 11/88 (12.5%), IR 7/83 (8.4%) success: ER 83/88 (94.3%), IR 75/83 (90.4%) indeterminate: ER 0/88 (0%), IR 1/83 (1.2%) relapse: ER 4/88 (4.6%), IR 6/83 (7.2%) failure: ER 1/88 (1.1%), IR 1/83 (1.2%) Clinically evaluable TOC: cure: ER 68/84 (81%), IR 64/78 (82.1%) improvement: ER 11/84 (13.1%), IR 6/78 (7.7%) success: ER 79/84 (94%), IR 70/78 (89.7%) indeterminate: ER 0/84 (0%), IR 1/78 (1.3%) relapse: ER 4/84 (4.8%), IR 6/78 (7.7%) failure: ER 1/84 (1.2%), IR 1/78 (1.3%) No sig differences in any clinical signs, sx	38 of 43 pts w/ sputum sample w/ target organism had organism susceptible to clari (only these pts eval'd) erad or presumed erad: ER 10/14 (71.4%), IR 19/24 (79.2%)	Investigators monitored ADR throughout study; lab assessments of serum biochem, hemat, medical hx, PE Severity assesment: mild: transient and easily tolerated by pt mod: caused pt discomfort and interrupted usual activities severe: caused considerable interference w/ usual activities and may have been incapacitating or life-threatening Causality assessed (method not described) Compliance assessed by pill counting	Total ADR: ER 79/117 (67.5%), IR 71/113 (62.9%) total # ADR reported: ER 222, IR 176 ADR considered possibly or probably med-related: ER 52/22 (23.4%), IR 43/176 (24.4%) most frequent ADR = GI (diarrhea, nausea, abd pain; specific #'s not reported) no clinically relevant changes in lab values, vital signs no sig differences in # ADR, severity of ADR causality: 170/222 (76.6%) events judged not related or probably not med-related Compliance (# pts who missed doses): ER 7, IR 16 (P=0.04)	Tx D/C'd due to ADR: ER 4, IR 1 (only 1 pt (ER) w/ ADR considered possibly or probably med-related

Evidence table 5. Summary of acute exacerbations of chronic bronchitis, acute bacterial exacerbations of chronic bronchitis (AECB, ABECB) trials

Author, Year **Country** **Trial Name**	**Comments**
Weiss, 2002 Canada	Note that some #'s in disposition of pts don't add up

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Adler, 2000 USA, Canada	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Bradbury, 1993 Ireland, Germany	method NR	NR	yes	yes	no	no	no	no	no	no	yes	fair
Castaldo, 2003 USA	yes	NR	yes	yes	yes (method NR)	NR	no	yes (attrition only)	no	yes	yes	fair
Cazzola, 1999 NR	method NR	NR	yes	yes	yes (method NR)	NR	no	no	no	no	yes	fair

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Adler, 2000 USA, Canada	screened NR eligible NR 627 enrolled	Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	none	NR	N/A	Industry - Abbott Laboratories	
Bradbury, 1993 Ireland, Germany	screened NR eligible NR 510 in entire study population AIECB 143 enrolled	Exclusion: cystic fibrosis, chronic diarrhea, peptic ulcer dx, any dx likely to affect drug absorption, terminally ill, pts receiving ergotamine, carbamazepine, or digitalis, drug- or alcohol-dependency, use of ABX w/in prior 2 weeks	none	NR	N/A	NR	
Castaldo, 2003 USA	screened NR eligible NR 86 enrolled 86 in study population	Exclusion: hx macrolide hypersens, clinical or radiographically demonstrated dx pneumonia, known malignancy or cardiopulmonary d/o, known HIV infxn, other long-standing causes of immunosuppression, use of ABX or investigational med w/in 30 days	none	NR	N/A	industry - Muro Pharmaceutical	
Cazzola, 1999 NR	screened NR eligible NR 80 enrolled	Exclusion: macrolide hypersens, ABX w/in 1 week entry, sig renal or hepatic impairment, hematologic abnormalities, underlying medical d/o that would interfere w/ eval, active TB, CF, lung carcinoma, HIV	none	NR	N/A	NR	

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Adler, 2000 USA, Canada	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	method NR	NR	yes	no	no	no	no	no	no	no	yes	poor
Gotfried, 2005 "North America"	method NR	NR	yes	yes	yes	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Hosie, 1995 UK, Ireland	method NR	NR	yes	yes	yes (method NR)	NR	no	yes (attrition, adherence only)	no	yes	yes	fair

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Adler, 2000 USA, Canada	screened NR eligible NR 627 enrolled	Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	none	NR	N/A	Industry - Abbott Laboratories	
Daniel, 1991 Austria, Belgium, Denmark, France, Finland, FRG, The Netherlands, Norway	screened NR eligible NR 181 in total study population 138 all bronchitis (# AIECB not individually stated)	Exclusion: chronic pulm dx w/o acute infective exac, life-threatening conditions, cystic fibrosis, receipt of ABX w/in 48h, any factor affect6ing drug absorption, drug or alcohol abuse, tx w/ warfarin, carbamazepine, or ergotamine	none	NR	N/A	industry - Pfizer	
Gotfried, 2005 "North America"	screened NR eligible NR 485 enrolled	Exclusion: severe or complicated RTI (including pneumonia), any resp condition that would confound eval (tumor, bronchiectasis, etc), sig renal or hepatic impairment, immunocompromised or oxygen-dependent pts, use of systemic ABX w/in 1 week (2 weeks for azi, 4 weeks for long-acting ABX) entry or concomitantly	none	NR	N/A	Industry - Abbott Laboratories	
Hosie, 1995 UK, Ireland	screened NR eligible NR 212 enrolled	Exclusion: any condition thought to preclude satisfactory eval, anticipated need for alternate ABX, use of ABX w/in 3 days entry, use of investigational med w/in 1 mo entry, CXR evidence of pneumonia w/in 24h entry, macrolide hypersens	none	NR	N/A	NR	

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Adler, 2000 USA, Canada	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	method NR	NR	yes	yes	yes	NR	yes	no	no	yes	yes	good

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Adler, 2000 USA, Canada	screened NR eligible NR 627 enrolled	Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	none	NR	N/A	Industry - Abbott Laboratories	
Nalepa, 2003 Czech Republic, Estonia, Finland, France, Germany, Latvia, Poland, South Africa, Ukraine, Uruguay	screened NR eligible NR 703 enrolled	Exclusion: severe or complicated RTI, severely compromised resp status, immunocompromised pts, sig renal or hepatic disease, use of systemic ABX w/in 2 weeks entry or concomitantly	none	NR	N/A	Industry - Abbott Laboratories	

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Adler, 2000 USA, Canada	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Sides, 1993 USA?	method NR	NR	yes	yes	yes (method NR)	NR	yes (method NR)	yes (attrition, adherence only)	no	yes	yes	fair
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	yes	NR	yes	yes	yes (method NR)	NR	yes (method NR)	yes (attrition only)	no	yes	yes	good

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Adler, 2000 USA, Canada	screened NR eligible NR 627 enrolled	Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	none	NR	N/A	Industry - Abbott Laboratories	
Sides, 1993 USA?	screened NR eligible NR 802 in study population ery: of 409 enrolled, 320 completed protocol, 81 qualified for post-therapy eval, 67 qualified for late post-therapy eval dir: of 393 enrolled, 321 completed protocol, 101 qualified for post-therapy eval, 80 qualified for late post-therapy eval	Exclusion: hx renal impairment (serum creatinine ≥ 133 µmol/L), hypersens to macrolides, use of ABX w/in 1 week entry, previous participation in an investigational study w/in 21 days entry	none	NR	N/A	NR	
Swanson, 2005 USA, Argentina, Brazil, Costa Rica, India, Chile, Canada, South Africa	screened NR eligible NR 322 enrolled	Exclusion: CXR dx of pneumonia, macrolide hypersens, use of systemic ABX w/in 7 days entry, any clinically sig diseases or lab abnormalities, any condition that may preclude eval, hepatic impairment, additional infxn requiring another ABX, use of investigational med w/in 4 weeks entry, prior enrollment in this trial	none	NR	N/A	Inustry - Pfizer, Inc.	

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Adler, 2000 USA, Canada	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Wasilewski, 1999 "North America"	yes	yes	yes	yes	yes	NR	yes	yes (attrition, adherence only)	no	yes	yes	good
Weiss, 2002 Canada	method NR	NR	yes	yes	no	no	no	yes (attrition, adherence only)	no	yes	yes	fair

Evidence table 6. Quality assessment of AECB, ABECB trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Adler, 2000 USA, Canada	screened NR eligible NR 627 enrolled	Exclusion: CXR evidence of: pneumonia, TB, empyema, lung abscess or tumor, acute infiltrates, bronchiectasis, or pleural effusion, sinusitis or other infxn requiring ABX, severe or complicated RTI or compromised resp status, macrolide hypersens, use of systemic ABX w/in 3 weeks entry, use of long-acting ABX w/in 30 days entry or investigational med w/in 4 weeks entry, sig renal or hepatic impairment, use of steroids or any immunosuppressive med, use of other systemic ABX	none	NR	N/A	Industry - Abbott Laboratories	
Wasilewski, 1999 "North America"	screened NR eligible NR 1057 enrolled (total in both studies) 499 enrolled in study 1 558 enrolled in study 2	Exclusion: any condition precluding eval of response, known or anticipated requirement for systemic ABX, macrolide hypersens, use of systemic ABX w/in 7 days entry, participation in a prior dir trial, participation in trial involving investigational med w/in 30 days entry, pts w/ pneumonia (dx'd by CXR)	none	NR	N/A	industri - Eli Lilly & Co.	
Weiss, 2002 Canada	screened NR eligible NR 233 enrolled	Exclusion: CXR evidence of pneumonia, active tuberculosis, lung tumor, use of systemic ABX w/in 14 days (4 weeks if long-acting), any other acute infxn, hx macrolide hypersens, hx CF or bronchiectasis, uncontrolled illness expected to influence clinical course, use of investigational med w/in 4 weeks, prior tx in this study, known sig hepatic or renal disease	none	NR	N/A	industry - Abbott Canada	

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Arguedas, 1997 Costa Rica	Randomized, double-blind Investigator randomization broken after assignment	Children 6 mo - 12 yr Sx consistent w/ uncomplicated AOM w/ otoscopic, tympanometric signs indicative of OM (flat response or excessive negative pressure) Exclusion: perforation of TM w/ or w/o drainage, prior placement of tympanostomy tube, hx macrolide hypersens, tx w/ ABX w/in 72h before enrollment, serious underlying disease, malabsorption syndromes or other GI disturbances precluding reliable tx w/ oral meds	azi 10 mg/kg/day qd x 3 days (max 500 mg/day) clari 15 mg/kg/day (bid) x 10 days	NR	Eval of sx and physical findings between days 3-5 and EOT (days 10-11), plus re-eval 28-32 days after EOT If any pt had tympanometric evidence of asymptomatic persistent middle ear effusion, pt not tx'd w/ any other ABX and re-eval'd 55-60 days after EOT; re-eval at any time if sx of disease recurred Each eval = hx, PE and ear eval, tympanogram Clinical outcomes: satisfactory response (complete resolution initial clinical sx w/ or w/o presence middle ear fluid) failure (bacteriologic (inability to sterilize MEF in pts w/ persistent ear drainage or w/ repeated tympanocentesis) and/or clinical (inability to clear initial clinical sx or persistent ear drainage by EOT) failure) recurrence (relapse vs reinfection)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics
Arguedas, 1997 Costa Rica	All pts underwent tympanocentesis at enrollment, prn after that Bacteriologic failure = inability to clear initial clinical sx or persistent ear drainage by EOT Timing not described (not systematically done)	Mean age: azi 50 mo, clari 50.4 mo Age range: azi 9-132 mo, clari 7-139 mo Gender (M/F): azi 24/26, clari 23/24 Ethnicity not reported	No sig differences in demographics, weight, laterality of disease, presenting sx, associated illness, bacteriology at enrollment

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical cure	Microbiological cure	Method of adverse effects assessment
Arguedas, 1997 Costa Rica	screened not reported eligibile not reported 100 enrolled 97 in study population	no w/d 3 enrolled but excluded (1 azi, 1 clari w/ resist bug (*P. aeruginosa*, *S. aureus*, respectively); 1 clari lost to f/u) 97 analyzed	Overall response: (unknown which visit these data from) clinical success: azi 50/50 (100%), clari 45/47 (95.7%) failure: azi 0/50 (0%), clari 2/47 (4.3%) relapse: azi 0/50 (0%), clari 0/47 (0%) reinfection: azi 0/50 (0%), clari 0/47 (0%) 2 clari failures: 1 = MEF w/ *S. pneumo*, removed on day 5 due to diffuse rash (possibly med-related), 1 febrile on day 6, developed tympanic membrane perforation, and tx'd w/ another ABX Persistent middle ear effusion: day 11-13: azi 35/50 (68%), clari 33/47 (70.2%) day 28-30: azi 8/50 (16%), clari 9/47 (19.1%)	None reported	Timing and method for ADR assessment not described; labs for neutropenia, thrombocytosis, LFTs (alkaline phosphatase, bilirubin) at enrollment, EOT Compliance monitored by daily parental med diary, determination of volume of med returned at day 3-5 and 10-11 visits, bioassay of urine; at EOT visit parents completed questionnaire related to compliance

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Arguedas, 1997 Costa Rica	No sig differences in ADR: nausea: azi 1/50 (2%), clari 2/47 (4.3%) vomiting: 1/50 (2%), clari 2/47 (4.3%) loose stools: 3/50 (6%), clari 6/47 (12.8%) rash: azi 0/50 (0%), clari 1/47 (2%) no sig differences in neutropenia, thrombocytosis, abnormal LFTs Compliance: > 90% med used: azi > 90% pts, clari > 90% pts positive bioassay: azi 95%, clari 95% Compliance per parent diary (clari n=46): child did not like taste: azi 0/50 (0%), clari 15/46 (33%) necessary to force child to take med:	Total: 2 clari: 1 removed on day 5 due to diffuse rash (possibly med-related), 1 febrile on day 6, developed TM perforation, and tx'd w/ another ABX	Note issue w/ clinical responses at indeterminate date

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Arguedas, 2005 USA, Costa Rica, Finland, Chile	Randomized, double-blind, double-dummy Multicenter	Children 6-30 mo. w/ AOM Pts w/ 1) at least 1 sx or sign consistent w/ AOM dx (sx of ear pain such as irritability or ear tugging or rubbing w/in 24h or clinical signs such as marked TM redness or fullness or bulging of TM) AND 2) presence of middle ear effusion, as evidenced by at least 2 of the following otoscopic findings: decreased or absent TM mobility documented w/ pneumatic otoscopy, yellow or white discoloration of TM, opacification of TM, or acute perforation (<24h) of TM w/ visible purulent material in ear canal Exclusion: tx w/ any other abx w/in 30 days pre-enrollment, sx or hx chronic or persistent OM (defined as ABX use in past 30 days for OM episode), tympanostomy tubes in place, hx pcn, pcn derivatives, or macrolide hypersens or intolerance, TM perforation of >24h, infxn known to be due to organism resistant to azi or amox, any other med condition considered clinically sig by investigators	azi 30 mg/kg x 1 + 10 days amox placebo (90 mg/kg/day; bid) azi placebo x 1 (30 mg/kg) + 10 days amox (90 mg/kg/day; bid) Each pt received study drug + placebo of comparator	Not described	MITT analysis Patients had to have received appropriate dx of AOM + at least 1 dose study med Bacteriologic MITT pts had to have at least 1 study-defined bug (*S. pneumo* , *H. flu* , *M. cat* , *S. pyog*) cx'd from MEF at baseline Day 1 = enrollment; clinical + otoscopic assessments repeated on day 4-6 (visit 2), EOT on day 12-14 (visit 3), EOS follow-up on day 25-28 (visit 4); interim visit any time lack of improvement, sig worsening, or recurrence of AOM sx; repeat tympanocentesis for cases considered failure or relapse Primary efficacy endpoint = clinical response at EOT for clinical MITT pts Secondary endpoints = clinical response at EOS for clinical MITT pts, clinical responses at EOS + EOT for bacteriologic MITT pts Clinical outcomes: cure (complete resolution of sx w/ or w/o presence of middle ear effusion) improvement (partial resolution of sx, w/ or w/o persistence of middle ear effusion but w/o need for additional ABX for AOM [EOT visit only]) failure (worsening of sx of infection, no response to therapy, or requirement for additional therapy for AOM [EOT visit only]) recurrence (pt previously evaluated as cured or imp

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	**Method of outcome assessment and timing of assessment - Microbiologic cure**	**Age Gender Ethnicity**	**Other population characteristics**
Arguedas, 2005 USA, Costa Rica, Finland, Chile	Bacteriologic MITT pts had to have at least 1 study-defined bug (*S. pneumo* , *H. flu* , *M. cat* , *S. pyog*) cultured from MEF at baseline No systematic microbiologic assessment (only in cases of failure/recurrence) Clinical responses differentiated by bug and by pcn MIC in pts w/ *S. pneumo* Susceptibility: study drugs + ampi (replaces amox for *H. flu*); *S. pneumo* + *S. pyog* tested for pcn suscept, and azi-resist strains tested for clnd suscept; *S. pyog* suscept to pcn considered suscept to amox; ampi breakpoints used for amox/*H. flu*	Mean age: azi 15.8 mo, amox 16.1 mo ≤ 24 mo age: azi 86%, amox 80.5% Gender ratio (M:F): azi 1.1, amox 1.6 Ethnicity not reported	No sig differences in demographics, weight, # siblings w/ hx AOM, # at daycare, # w/ age < 6 mo at 1st AOM, household smoke exposure, pacifier use, # received pneumococcal vaccine, risk factors for pcn-resist *S. pneumo* , bacteriology at enrollment

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical cure	Microbiological cure	Method of adverse effects assessment
Arguedas, 2005 USA, Costa Rica, Finland, Chile	screened not reported eligible not reported 313 enrolled 312 in study population	no w/d 1 randomized but no study drug 3 azi w/ no assessments at EOT, EOS (1 incorrect dx, 2 no show up for f/u) 3 amox w/ no assessments at EOT, EOS (lost to f/u) Clinical MITT: azi 155, amox 151 Bacteriologic MITT: EOT azi 105, amox 105; EOS azi 102, amox 74	MITT: (cure or improve): EOT, all: azi 130/155 (84%), amox 127/151 (84%) EOT, ≤ 2 yr: azi 109/133 (82%), amox 99/121 (82%) EOS, all: azi 117/152 (77%), amox 117/151 (78%) EOS, ≤ 2 yr: azi 98/130 (75%), amox 91/121 (75%) Bacteriologic MITT (cure or improve): EOT, all pathogens: azi 84/105 (80%), amox 87/105 (83%) EOS, all pathogens: azi 75/102 (73.5%), amox 77/104 (74%) azi-suscept *S. pneumo* : EOT 28/33 (85%), EOS 25/30 (81%) azi-resist *S. pneumo* : EOT 6/9 (67%), EOS 5/8 (63%)	Not reported (of 39 bacteriologic MITT w/ clinical failure at day 12-14, 10 azi, 9 amox had f/u tympanocentesis; of 10 w/ recurrence at day 25-28, 1 azi, 1 amox had f/u tympanocentesis)	All pts w/ at least 1 dose study med Tx-relatedness judged by investigators as related or possibly related to study med Case report form included reports of diarrhea or loose stools as judged by parental diary or pt hx at each visit Severity categorized as mild, mod, severe Compliance verified w/ parental diaries, inspection of med bottles at EOT (compliance if 80-120% of study med received)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Arguedas, 2005 USA, Costa Rica, Finland, Chile	Overall tx-related: azi 19.6%, amox 28.6% (P=0.064) GI most common diarrhea: azi 8.2%, amox 17.5% (P=0.017) vomiting: azi 8.2%, amox 8.2% abd pain: azi 3.9%, amox 2% rash: azi 2.5%, amox 2.6% No serious ADR, no D/C due to ADR, all resolved Compliance: azi 100%, amox 90% (P=0.001)	3 azi no show up for f/u (? reason) No w/d due to ADR	Equivalence (noninferiority) trial Note that clinical responses also differentiated by bug and by pcn suscept in *S. pneumo* (data not included here)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Coles, 1993 UK	Single-blind (investigator-blind), randomized, phase 3 Multicenter	Children 1-12 yr At least 2 of the following: otalgia, fever, acute hearing loss, tugging or rubbing of the ear; or URTI w/ at least 1 of the following: hyperemia, decreased mobility or bulging of TM, loss of TM "landmarks", or acute otorrhea not caused by external otitis; otological exam had to be consistent with presence of fluid in middle ear Exclusion: at risk of pregnancy, hx macrolide, pcn, or beta-lactam hypersens, evidence of or suspected hepatic or renal impairment, suspected or dx'd glandular fever, evidence of chronic, suppurative OM, currently receiving clari or amox at study day 1, received systemic ABX w/in 3 days prior to study drug administration, received topical ABX to tx this infection prior to study drug administration, had investigational or long-acting ABX w/in 4 weeks prior to study drug administration, were receiving concurrent theophylline, carbamazepine, ergotamine, digitalis, or warfarin (unless adequate monitoring of these drugs possible)	clari 125 mg bid (wt ≤ 25 kg) or 250 mg bid (wt > 25 kg) x ~ 5 days amox 125 mg tid (wt < 25 kg) or 250 mg tid (wt ≥ 25 kg) x ~ 5 days	Not described	Clinical evals prior to therapy on day 1 and at EOT on days 6-9 (visit 2), w/ f/u eval between days 28-32 (visit 3; or earlier if recurrence occurred) to determine clinical recurrence for pts assessed as clinical cure or improvement at EOT At study entry, following clinical signs and sx assessed and graded as absent, mild, mod, or severe: otalgia, hyperemia of TM, irritability; bulging of TM and acute otorrhea noted as present or absent; mobility of TM noted as normal or abnormal; TM landmarks classified as clearly present, partially obscured, or obscured; overall clinical condition classified as good, fair, or poor; infection status classified as mild, mod, or severe At visit 2: med hx update, physical exam, vital signs, assessment of signs and sx Clinical outcomes: cure (pre-tx signs and sx resolved/absent) improvement (signs and sx improved but not resolved) failure (signs and sx worsened or not improved) indeterminate (pt unavailable for or refused assessment) success (cure+improvement) All cures and improvements assessed at visit 3 for recurrence or relapse
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	Open-label Multicenter	Children 2-12 yr Clinical dx AOM (established by hx, clinical findings, and, when possible, bacteriologic confirmation) Exclusion: tx w/ any other ABX in 2 weeks prior (unless tx failure documented), tx w/ any investigational drug in past month, any infxn requiring additional ABX, hx chronic diarrhea or other GI d/o affecting drug absorption, terminal illnesses or other conditions that could prevent study completion, known macrolide, pcn, or azi hypersens, were receiving concurrent ergotamine, carbamazepine, or digitalis	azi 10 mg/kg qd x 3 days amox 10 mg/kg tid x 10 days (> 20kg = 250 mg tid)	None systematically described 26 azi, 23 amox used concurrent meds ("mainly analgesics or drugs acting on resp system, such as decongestants, cough mixtures, anti-histamines"); 1 amox pt received ear drops w/ phenazone, benzocaines; no concurrent ABX	Visit 1 = before start of tx, visit 2 = day 2-4, visit 3 = day 11-13 Clinical eval at each visit: fever, lethargy, earache, diminished light reflex, erythema or perforation of TM Clinical outcomes: cure improvement failure relapse (compared w/ previous assessment) Clinical response recorded at visit 3 only (EOT)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics
Coles, 1993 UK	Not performed	Mean age, all pts: clari 5.8 yr, amox 5.3 yr Mean age, evaluable pts: clari 5.7 yr, amox 5.2 yr Age range, all pts: clari 1-12.5 yr, amox 1-11.7 yr Age range, evaluable pts: clari 1-12.5 yr, amox 1-11.7 yr Gender (M/F), all pts: clari 54/78, amox 70/57 Gender (M/F), evaluable pts: clari 47/67, amox 58/47 Ethnicity: caucasian, afro-caribbean, asian, other	Stat sig difference in gender distribution between groups (all pts only) No sig differences in age, weight, height, ethnicity, # middle ear infxns in previous 12 mo, # days since onset of this episode OM, infxn status, overall clinical condition, concomitant meds, # receiving systemic ABX after EOT (usually for coincidental RTI or recurrence of OM)
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	Bacteriologic response recorded at visits 2, 3 Responses: eradication, persistence, superinfection, recurrence, reinfection, non-evaluable	Mean age: azi 4.3 yr, amox 4.1 yr Age range: azi 1.8-12 yr, amox 2-12 yr Gender (M/F): azi 45/32, amox 34/43 Ethnicity not reported	azi 8/77 dx'd w/ recurrent OM (all 8 w/ acute exac), amox 5/77 dx'd w/ recurrent OM (7/8 w/ acute exac) No sig differences in baseline severity (signs, sx)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical cure	Microbiological cure	Method of adverse effects assessment
Coles, 1993 UK	screened not reported eligible not reported 259 enrolled 219 in study population	6 clari prematurely D/C'd (4=insufficient improvement in condition, 1=refused med on day 3, 1=developed pharyngitis and w/d by investigator) 5 amox prematurely D/C'd (3=ADR, 1 lost to f/u, 1 w/d by investigator when parent administered concurrent pcn V on day 4) 219 analyzed	Evaluable pts: cure: clari 91/114 (79.8%), amox 71/105 (67.6%) success: clari 110/114 (96.5%), amox 101/105 (96.2%) recurrences: 6/96 (6.3%), amox 5/83 (6%) ITT: cure: clari 77%, amox 68% (pt #'s not reported) success: clari 95%, amox 94% (pt #'s not reported) No clinically or stat sig differences between clari, amox in rates of resolution of clinical signs and sx due to OM	Not reported	ADR classified as: mild: easily tolerated mod: caused discomfort and interrupted daily activities severe: caused considerable interference w/ activities and could have been incapacitating or life-threatening Causality: not related: not previously reported for med class, temporal, or due to alternate etiology remotely related possibly related probably related definitely related: commonly reported for med class, temporally related, re-appearing on rechallenge, and not due to alternate etiology
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	screened not reported eligible not reported 154 in study population	no w/d no lost to f/u 154 analyzed	Overall response: cure: azi 61/77 (79%), amox 45/77 (58%) improved: azi 15/77 (20%), amox 28/77 (37%) failure: azi 1/77 (1%), amox 4/77 (5%) AOM: cure: azi 57/69 (83%), amox 43/72 (63%) (P=0.03) improved: azi 11/69 (16%), amox 25/72 (35%) failure: azi 1/69 (1%), amox 4/72 (5%) Recurrent OM: cure: azi 4/8 (50%), amox 2/5 (40%) improved: azi 4/8 (50%), amox 3/5 (60%)	Stat eval not possible because no pathogen isolated from 10 or more pts in either group	Monitored at each visit and for 35 days after EOT All observed, volunteered ADR recorded and classified as mild, mod, severe Causality assessed (by unknown method), all ADR deemed possibly tx-related or w/ unknown causality included in results Labs (hemat, biochem, urinalysis) at visits 1, 3; any judged to be possibly tx-related included in results

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Coles, 1993 UK	any ADR: clari 21/132 (16%), amox 22/127 (17%) possibly, probably, or definitely related: clari 4/132 (3%) w/ total 5 ADR (1 definitely related = intermittent mild taste perversion), amox 8/127 (6%) w/ total 9 ADR (1 probably related = mod diarrhea) Amox: 1 diarrhea severe, 1 vomiting severe total GI: clari 2/132 (1.5%), amox 7/127 (5.5%) diarrhea: clari 2/132 (1.5%), amox 3/127 (2.4%) nausea: clari 0/132 (0%), amox 1/127 (0.8%) vomiting: clari 1/132 (0.8%), amox 4/127 (3.1%)	0 clari D/C'd due to ADR 3 amox D/C'd due to ADR (1 each mod vomiting, mod diarrhea, mild eczema)	No microbiological assessment at all in this study (even pre-study confirmation)
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	Possible tx-related ADR: azi 2/77 (3%) [all abd pain], amox 3/77 (4%) [all diarrhea] No serious ADR except 1 amox w/ serious diarrhea, no D/C due to ADR No lab ADR	None for any category	Note pts w/ recurrent OM (although results w/ and w/o these pts reported)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Muller, 1993 Germany, Ireland	Randomized; blinding not reported Multicenter	Pts > 12 yr AOM, sinusitis, pharyngitis, tonsillitis (multiple conditions study) Dx made based on clinical hx, physical findings	azi 500 mg qd x 3 days clari 250 mg bid x 10 days	NR	Eval at day 10-14 Clinical outcomes: cure: disappearance of clinical signs, sx improvement: improvement in or partial disappearance of signs, sx failure: no change or worsening signs, sx relapse: improvement or cure followed by worsening
Pukander, 1993 Finland	Single-blind (investigator-blind), randomized, phase 3 Multicenter	Children 1-12 yr Diagnostic criteria (based on hx, physical exam) of AOM: at least 1 of otalgia, irritability, tugging or rubbing of ear(s), URTI, vomiting, diarrhea, or fever, in association w/ otoscopic signs such as hyperemia, decreased mobility or bulging of TM, or loss of TM "landmarks" Exclusion: tx w/ any systemic ABX w/in 7 days before enrollment through EOS, topical ABX ear drop tx, investigational drug or long-acting ABX (e.g., benzathine pcn) use w/in 4 weeks before enrollment, prior participation in this trial, hx macrolide or beta-lactam hypersens, presece of major systemic disease, evidence of chronic, suppurative OM, another episode of AOM w/in past 28 days, evidence of perforated TM	clari 7.5 mg/kg bid (max 500 mg bid) x 7-10 days amox 20 mg/kg bid (max 750 mg bid) x 7-10 days	Not described	Pre-tx visit, 2 f/u visits: w/in 48h and 10-14 days after last dose of study med Clinical outcomes: cure (pre-tx signs and sx had resolved and middle ear effusion-free) improvement (pre-tx signs and sx improved by not completely resolved) failure (pre-tx signs and sx did not improve or worsened, and effusion present in middle ear) indeterminate (response could not be determined, or study med received for < 3 full days)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics
Muller, 1993 Germany, Ireland	Eval at day 10-14 Outcomes: eradication: eradication or no culturable material (absence of cough) superinfection: new pathogen that requires treatment persistence: persistance of all pathogens recurrence or reinfection not evaluable: no organism isolated	Mean age: azi 40.6 yr, clari 38.8 yr Gender (M/F): azi 117/74, clari 109/80 Ethnicity not reported	# pts/indication: otitis: azi 34, clari 36 sinusitis: azi 75, clari 74 pharyngitis/tonsillitis: azi 82, clari 79
Pukander, 1993 Finland	All pts underwent tympanocentesis w/in 48h before 1st dose study med; repeated prn as clinically indicated No systematic microbiologic eval	Age, gender, ethnicity not reported	Not reported

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical cure	Microbiological cure	Method of adverse effects assessment
Muller, 1993 Germany, Ireland	screened not reported eligible not reported 380 in study population	w/d: 23 lost to f/u: 11 357 analyzed	Overall AOM: cure: azi 26 (79%), clari 26 (74%) improved: azi 18%, clari 23% failed: azi 3%, clari 3%	Day 10-14, AOM: eradicated: azi 3/3 (100%), clari 6/6 (100%)	ADR volunteered by pts
Pukander, 1993 Finland	screened not reported eligible not reported 79 enrolled 47 in study population	32 excluded due to no bacterial growth in pre-tx MEF or otherwise did not fulfill all inclusion criteria 1 amox prematurely D/C'd tx	Overall: cure: clari 10/27 (37%), amox 11/20 (55%) improvement: clari 15/27 (56%), amox 7/20 (35%) success (cure + improvement): clari 25/27 (93%), amox 18/20 (90%) effusion-free w/in 2 weeks of start tx): clari 17/27 (63%), amox 10/20 (50%)	Not reported	Not reported n=79 (all enrolled)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Muller, 1993 Germany, Ireland	Overall ADR: azi 16/191 (8%), clari 14/189 (7.4%) abd pain: azi 5, clari 0 diarrhea: azi 5, clari 2 dyspepsia: azi 0, clari 1 gastritis: azi 0, clari 2 hiccups: azi 0, clari 1 nausea: azi 2, clari 3 vomitiing: azi 1, clari 1	3 azi (2 abd pain, 1 vomiting) 3 clari (nausea, pruritis, MI (causality unknown))	
Pukander, 1993 Finland	Overall (n=79): any ADR: clari 10/39 (26%), amox 7/40 (18%) abd pain: clari 3/39 (7.7%), amox 3/40 (7.5%) diarrhea: clari 3/39 (7.7%), amox 3/40 (7.5%) No sig differences in labs reported (labs not specified)	1 w/d (amox) 1 w/d due to ADR (amox - mod skin rash)	Note that clinical responses also differentiated by bug (data not included here)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Study design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of outcome assessment and timing of assessment - Clinical cure
Scholz, 1998 Germany	Double-blind, randomized Multicenter	Children 6 mo - 11 yr Newly dx'd AOM (onset of sx during 4 days before entry) Diagnostic criteria: 1) evidence middle ear effusion as determined by tympanometry or presence of otorrhea of < 24h duration, not due to otitis externa or chronic otitis, plus 2) otoscopic evidence middle ear inflammation and 3) at least 1 of the following signs or sx: ear pain, tugging/rubbing of ear, fever, or acute hearing reduction caused by AOM Otoscopic evidence of middle ear inflammation defined as presence of 1 or more of the following TM abnormalities: hyperemia, bulging or cloudiness of TM, or fluid level and/or bubbles indicative of effusion Exclusion: hx AOM w/in 4 weeks before entry, otorrhea for > 24h, presence of tympanostomy tubes or ay other sign or sx chronic OM or OM w/ effusion, ABX w/in 7 days prior to entry (4 weeks for ABX w/ depot affect), prior enrollment in this study, participation in another clinical trial w/in past 30 days, beta-lactam or macrolide hypersens, pre-existing severe illness such as Down's syndrome, cleft palate, craniofacial d/o's, or immunodeficiency, c	ery estolate 40 mg/kg/day (bid) amox 50 mg/kg/day (bid) All tx for 10 days Suspensions equal in taste, smell, color, and volume per dose	decongestant nasal drops, apap, and expectorants in case of concurrent URTI	Adapted from IDSA guidelines At entry, f/u visits: hx and PE, otoscopy, tympanometry performed by same physician (tympanogram assessed by 1 author) f/u: mid-tx (day 3-4), EOT (day 9-11), 5 weeks after enrollment; additional assessments prn when sx of ear disease developed or persisted Pts evaluable for efficacy if met criteria for compliance, had baseline tympanogram at at least 1 ear c/w AOM, returned for all f/u visits Clinical outcomes: (assessed on day 9-11) success (resolution all signs, sx of AOM and resolution or marked improvement of otoscopy findings, regardless of presence of residual middle ear effusion) failure (1 or more of following conditions: worsening or lack of resolution of signs and sx, lack of marked improvement of otoscopy findings, new clinical or otoscopic signs or sx of AOM, change of ABX or tympanocentesis deemed necessary, complications of AOM during tx (≤ 24h after initiation of tx) or f/u recurrence (reappearance of AOM during f/u after sx-free interval) early relapse (recurrence occuring w/in 3 days after EOT (days 11-13))

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Method of outcome assessment and timing of assessment - Microbiologic cure	Age Gender Ethnicity	Other population characteristics
Scholz, 1998 Germany	Not performed	Mean age: ery 52.5 mo, amox 50.5 mo Age range: ery 1-122 mo, amox 7-117 mo Gender (M/F): ery 77/64, amox 85/54 Ethnicity not reported	No sig differences in demographics, use of concomitant meds, bilaterality of AOM, hyperemia of TM, clinical and otoscopic findings at entry, weight

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical cure	Microbiological cure	Method of adverse effects assessment
Scholz, 1998 Germany	screened not reported eligible not reported 302 enrolled 280 in study population	10 ery, 12 amox excluded due to protocol violations (8 w/ nonpermitted concomitant med, 7 tympanograms at entry not consistent w/ AOM, 2 lost to f/u, 2 D/C'd tx due to ADR, 2 noncompliant, 1 < 6 mo age)	Overall: clinical success: ery 132/141 (93.6%), amox 133/139 (95.7%) failure: ery 9/141 (6.4%), amox 6/139 (4.3%) recurrence: ery 8/141 (5.7%), amox 7/139 (5%) No sig differences in ear pain or rubbing tugging, fever, hyperemia of TM, bulging of TM, cloudiness of TM	Not reported	Parents questioned at each visit Any ADR recorded and assessed for duration, outcome, relationship to study med (causality assessment process not described) Compliance verified w/ parental diaries (compliance if ≥ 70% of study med received)

Evidence table 7. Summary of otitis media trials

Author, Year Country Trial Name	Adverse effects reported	Total withdrawals; withdrawals due to adverse events	Comments
Scholz, 1998 Germany	ADR classified as certainly, probably, or possibly related: ery 8/141 (5.3%), amox 11/139 (7.3%) ery: GI most common, amox: exanthematic reactions most common no serious or previously unknown ADR D/C due to ADR: ery 0/141 (0%), amox 5/141 (3.5%; 3 in efficacy analysis) No sig differences in compliance	10 ery, 12 amox excluded 5 amox D/C'd tx due to ADR; 3 included in efficacy analysis because they received at least 70% med	

Evidence table 8. Quality assessment of otitis media trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
	Internal Validity											
Arguedas, 1997 Costa Rica	yes	NR	yes	yes	yes, but broken after assignment made (method NR)	NR	yes (method NR)	yes (attrition, adherence only)	no	yes	yes	poor
Arguedas, 2005 USA, Costa Rica, Finland, Chile	method NR	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	yes	yes	fair
Coles, 1993 UK	method NR	NR	yes	yes	yes (method NR)	NR	no	yes (attrition, adherence only)	no	yes	no	fair

Evidence table 8. Quality assessment of otitis media trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
	External Validity						
Arguedas, 1997 Costa Rica	screened NR eligibile NR 100 enrolled 97 in study population	Exclusion: perforation of tympanic membrane w/ or w/o drainage, prior placement of tympanostomy tube, hx sig reaction to macrolide, tx w/ ABX w/in 72h before enrollment, serious underlying disease, malabsorption syndromes or other GI disturbances precluding reliable tx w/ oral meds	none	NR	yes	industry - Pfizer	
Arguedas, 2005 USA, Costa Rica, Finland, Chile	screened NR eligible NR 313 enrolled 312 in study population	Exclusion: 1) tx w/ any other abx w/in 30 days pre-enrollment, 2) sx or hx chronic or persistent OM (defined as ABX use in past 30 days for OM episode), 3) tympanostomy tubes in place, 4) hx hypersensitivity or intolerance to pcn, pcn derivatives, or macrolide, 5) tympanic membrane perforation of >24h, 6) infxn known to be due to bug resistant to azi or amox, 7) any other med condition considered clinically sig by investigators	none	NR	yes	industry - Pfizer	
Coles, 1993 UK	screened NR eligible NR 259 enrolled 219 in study population	Exclusion: at risk of pregnancy, hx hypersens to macrolide, pcn, or beta-lactam, evidence of or suspected hepatic or renal impairment, suspected or dx'd glandular fever, evidence of chronic, suppurative OM, currently receiving clari or amox at study day 1, received systemic ABX w/in 3 days prior to study drug administration, received topical ABX to tx this infection prior to study drug administration, had investigational or long-acting ABX w/in 4 weeks prior to study drug administration, were receiving concurrent theophylline, carbamazepine, ergotamine, digitalis, or warfarin (unless adequate monitoring of these drugs possible)	none	NR	yes	NR	

Evidence table 8. Quality assessment of otitis media trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality rating
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	not randomized	NR	yes	yes	no	NR	no	yes (attrition only)	no	yes	no	poor
Muller, 1993 Germany, Ireland	yes	NR	yes	yes	no	NR	no	yes (attrition only)	no	no	yes	fair
Pukander, 1993 Finland	method NR	NR	unknown	yes	yes (method NR)	NR	no	yes (attrition only)	no	no	yes	poor
Scholz, 1998 Germany	yes	NR	yes	yes	yes (method NR)	NR	yes	yes (attrition, adherence only)	no	no	yes	good

Evidence table 8. Quality assessment of otitis media trials

Author, Year Country	Number screened / eligible / enrolled	Exclusion criteria	Run-in/ washout	Class naïve patients only	Control group standard of care	Funding	
Mohs, 1993 Guatemala, Costa Rica, Panama, Egypt	screened NR eligible NR 154 entered study 154 evaluated	Exclusion: tx w/ any other ABX in 2 weeks prior (unless tx failure documented), tx w/ any investigational drug in past month, any infxn requiring additional ABX, hx chronic diarrhea or other GI d/o affecting drug absorption, terminal illnesses or other conditions that could prevent study completion, known hypersens to macrolides, pcns, or azi	none	NR	yes	NR	
Muller, 1993 Germany, Ireland	screened NR eligible NR 380 in study population		none	NR	yes	NR	
Pukander, 1993 Finland	screened NR eligible NR 79 enrolled 47 in study population	Exclusion: tx w/ any systemic ABX w/in 7 days before enrollment through EOS, topical ABX ear drop tx, investigational drug or long-acting ABX (e.g., benzathine pcn) use w/in 4 weeks before enrollment, prior participation in this trial, hx hypersens to macrolides or beta-lactams, presece of major systemic disease, evidence of chronic, suppurative OM, another episode of AOM w/in past 28 days, evidence of perforated tympanum	none	NR	yes	NR	
Scholz, 1998 Germany	screened NR eligible NR 302 enrolled 280 in study population	Exclusion: hx AOM w/in 4 weeks before entry, otorrhea for > 24h, presence of tympanostomy tubes or ay other sign or sx chronic OM or OM w/ effusion, ABX w/in 7 days prior to entry (4 weeks for ABX w/ depot affect), prior enrollment in this study, participation in another clinical trial w/in past 30 days, hypersens to beta-lactam or macrolide, pre-existing severe illness such as Down's syndrome, cleft palate, craniofacial d/o's, or immunodeficiency, concurrent acute disease (other than URTI), any CI to either study med	none	NR	yes	industry - Infectopharm	

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Adults:										
Bachand, 1991 USA	R, DB, multicenter	positive cx, age not specified	clari 250 q12 * duration not reported vs pen VK 250 q6h	2-10d post tx, cure:s/s resolved improvement: improved s/s, not resolved failure: s/s not improved or worsened indeterminate relpase/recurrance: resolved but reappeared	2-10d post tx, 15-56d cure: eradicated failure: same organism isolated indeterminant relapse: eradicated, but back reinfection: eradicated, then new serologic isolate	clari vs pen 27.6(12-57) vs 27.1(12-62) 41F/24M vs 48F/15M white: 52 vs 54pts black: 9 vs6pts asian: 1 vs 1 pt other: 3 vs 2pts	most treated >11d more lymph node tenderness clari group: 97% (37/38)vs 76% (32/42), p=0.008 all other s/s similar - not likley important	nr,nr,128	nr,nr,90 26 stopped premature, 38 excluded excluded if R to drug (n=1 pcn)	2-10d post tx clari vs pen cure: 37/43(86%) vs 36/47 (77%) improve: 9% vs 15% failure: 2 vs 4% NS
Hooten 1991 USA	multicenter, randomized	>=16 yrs, +cx, s/s	azi 500x1d then 250 for 4d vs pen 250mg QID for 10d	days 6, 11, 18, 30 cure: no evidence infection improved: incomplete resolution failure: no apparent clinical response by day 11	day 11 cure: negative cx	"similar", NR		nr,nr,346	104,nr,242 5 d/c because R azi 17% cx neg, 9% missed visits or sensitivity unavailable	azi vs pen cure:86.8 vs 77.8% improved: 12.6% vs 21.1% failed: 0.7% vs 1.1%
Kaplan 2001 USA	investigator blinded multicenter randomized	>=12 years s/s, w/+ throat swab, f/u cx	clari 250mg BID for 10d vs azi 500mgx1 day then 250mg po QD for 4 days	13 to 19 days post, and 28-38 d post not defined	13 to 19 days post, and 28-38 d post eradication: - cx both visits failure: + cx at either	26.8 (12-61)clari 26.1 (12-59) azi 153 M, 239 F 359 white, 13 black, 20 other no differences		NR/NR/525	133/NR/392 (80 neg cx)	clari vs azi cure 92% vs 92%, NS

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Adults:					
Bachand, 1991 USA	Day 2-10 post clari vs pen cure:38/43(88%) 43/47(91%) NS failure: 12% vs 9%, NS	COSTART, patient reports	overall AE clari vs pen 26.2% vs 17.5% drug related 10.8 vs 3.2% drug-related GI GI 19/65 (29.2) clari, 8/63 (12.7%) PCN, p<=0.05	clari 3pts (only 1 deemed drug related)	98% S organisms
Hooten 1991 USA	azi vs pen eradication: 90.8 vs 95.6 recurrance: 9.6 vs 11.9%	NR	azi vs pen all AE: 16.6% vs 1.7%, p<0.001 GI: 32/229 vs 2/117 diarrhea: 12/229 vs 0 nasusea: 6/229 vs 0 abd pain: 7/229 vs 2/117	azi vs pen w/d due to AE: 4 (1.7%) vs 1 (0.9%), NS	<50% taken drug= unevaluable
Kaplan 2001 USA	13-19 day visit clari vs azi 95% vs 88%, p=0.019 28-38 day visit clari vs azi 91% vs. 82%, p=0.012	not reported	not reported	not reported	sensitivities to macrolides simliar 98%clari,97%azi

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Levenstein 1991 Australia,Chile,South Africa, New Zealand	randomized, double blind, multicenter	13-59y, s/s, cx+	250mg clari q12 for 8-10d vs 250mg pen q6h for 10-14d	2-10d post therapy, day 15-56d cure: s/s resolved improved: not totally resolved failure: not improved or worsened indeterminate: not assigned "due to non-compliance or other reasons"	2-10d post therapy, day 15-56d cure: not positive failure: culture remained positive indeterminate: not confirmed	Evaluable pts only age: 13-59 clari vs pen 3F/64M vs 3F/55M "no differences" age, race	NR	nr,nr,243	118,nr,125 19 no positve cx, 2pts clari group d/c b/c "ineffective" 118 removed from efficacy analysis 82 neg culture	2-10d post tx clari vs pen cure:96 vs 98% improved: 4 vs 2% failure: 0 vs 0% indeterminate: 0vs0%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Levenstein 1991 Australia,Chile,South Africa, New Zealand	2-10d post tx clari vs pen cure:100 vs 97% failure: 0 vs 3% day 15-56 cure: 98 vs 98% failure: 2 vs 2%	patient report	Any AE clari vs pen 6% vs 9% Digestive: 2 vs 1%	none	

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Portier 2002 France	multicenter, randomized, open-label	12-40 years, +cx	clari modified release 500mg QD * 5d vs 590mg (1MU) pen TID for 10d	3d post tx end (d8 or 13), day 30 cure: disppearance s/s failure: not improved or aggravated recurrance: reappearance at day 30 indeter ITT: one dose mITT: +cx only PP: all evaluable	3d post tx end (d8 or 13), day 30 eradication: neg at 3d failure: positive at day3 recurrance: + after neg indeterminate	clari vs pen 27.8 vs 26.8 M;F ratio: .62 vs .68	similar s/s	nr,nr,349 349ITT, 303 mITT	nr,nr,239 PP=239 29 neg cx, 35 protocol deviation	3d post tx ITT clari vs pen cure:88.1 vs 92.4% failure: 5.6 vs 3.5% indeterminate: 1.1 vs 0% missing(not defined): 5.1 vs 4.1% 3d PP cure:95.2 vs 97.3% failure: 4.8 vs 2.7% Day30 ITT cure: 78.8% vs 80.3 recurrance: 4.6 vs 2.0% indeter: 3.3 vs 0.6% missing: 13.2 vs 17.1% PP day 30 91.7 vs 98.1% recurrance: 5.0 vs
Scaglione 1990 Italy	open label randomized # centers not reported	>=12 years s/s, w/+ culture GABHS organism sensitive	clarithromycin 250mg bid vs erythromycin stearate 500mg bid for 10 days	day 14-16 and day 29-35 clinical s/s of infection culture cure: s/s resolved improvement: s/s improved not resolved failure: s/s not improved or worsened indeterminate	day 14-16 and day 29-35 eradication: cx neagtive both time frames eradication with relapse or re-infection: 1st culture negative second positive indeterminate	43.97 (range NR) Gender 149 M, 91F Ethnicity NR (stated equal)		# screened NR/# eligible NR/ 240 enrolled	# withdrawn NR/ # lost to f/u NR/230 clinical evaluable/207 micro evaluable	clari vs ery clinical cure: 80.0% vs 80.0% clinical improvement: 16.5% vs. 13.9% clinical failure: 0.9% vs. 5.2% indeterminate: 2.6% vs. 0.9%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Portier 2002 France	3d post mITT clari vs pen cure: 82.8% vs 83.6% failure: 7.9 vs 7.9% indeterminate:0.6 vs 2.0% missing: 8.6 vs 6.6% PP 3d cure:94.4 vs 92.0% failure:5.6 vs 7.1% Day 30 ITT cure: 70.2 vs 69.1 recurrance: 8.6 vs 5.3% indeterminate: 4.6 vs 2.6% missing: 16.6 vs 23.0% PP d30 cure: 85.6 vs 93.2% recurrance: 10.2	NR	AE clari vs pen 26% vs 18%, p+0.073	1 in each group d/c due to AE	80% drug needed to be evaluable 9.7% clari R isolate 28% eradication in 14 clari R isoltes
Scaglione 1990 Italy	clari vs ery eradication 97.3% vs 92.5% eradication with relapse or persistance 2.7% vs. 6.6%	patient report (not specified who intiated) laboratory monitoring	clari vs. ery epigastric pain 6 vs 7pts nausea 1 vs. 4 pts vomiting 1 vs 1 pts	clari vs. ery total w/d NR total w/d due to AE 1 (0.8%) vs 8 (6.7%) NR	needed 6 doses to be clinically evaluable

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Schrock 1992 USA	randomized, investigator blind, multicenter	>=12years, +cx or immunoassay, s/s	clari 250 q12 * 10d vs pen VK 250 q8h* 10d	4-6d post tx, 19-25 post cure:s/s resolved improvemement: improved, not resolved failure: unchanged or worsened Indeterminate	4-6d post and 19-25d post eradicated persistence: same isolate recurrant: neg then same serology pos at 19-25 re-infection: neg then new serologic organism Indeterminate	clari vs pen 99F/127M vs 84F/143M 30 (12-62)Y vs 30 (12-64)y NR	same s/s & severity	nr,nr,453	97,NR,356 53 no pos cx	clari vs pen 4-6d post tx cure: 89 vs 85% improved: 8 vs 11% failure: 3 vs 3% indeter:0 vs 1% "success": 97 vs 97% 19-25 days post cure:93 vs 88% improved 1 vs 1% failure: 0 vs 0 relapse: 6 vs 10% indeter: 3 vs 10% "success": 94 vs 90%, NS
Stein 1991 USA	randomized, double blind, multicenter	>=12 years, +cx	clari 250 q12 * 10d vs pen VK 250 q6h* 10d	d 14-16 and 29-35 cure: complete resolution s/s improved: considerable resolution s/s failure: no improvement	day 14-16 and 29-35 present absent	clari vs pen 28(12-54) vs 29 (12-58) 24M/41F vs 15M/48F NR	similar s/s, 13 calri pt fever vs 6 pen pts	nr,nr,128	nr,nr,97	end of study clari vs pen cure:79 vs 79 improvement: 2 vs 4% failure: 4 vs 6% recurrance: 15 vs 11%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Schrock 1992 USA	clari vs pen 4-6d post cure: 95 vs 87%, P=0.009 failure: 5 vs 13% indeter: 2 vs 5% day 19-25 post cure: 94 vs 88% failure: 0vs0% reinfection: 1 vs 1% recurrance: 6 vs 11% indeter: 12 vs 31%	NR	All AE clari vs pen 38 vs 36%		Evaluable if 7d tx. D/C due to clincial failure or AE included in efficacy analysis 96% S to both drugs
Stein 1991 USA	end of study clari vs pen eradication: 87 vs 85% persistence: 2 vs 0% recurrance: 11 vs 15%	Investigator questioning	All possible AE clari vs pen 38% vs 21%, p<0.05 diarrhea 15 vs 2%, p<0.01 GI upset: 9 vs 2% nausea: 9 vs 10% vomitting: 3 vs 0%	1 clari pt, 0 pen d/c	Evaluable if 7d tx d/c if R isolate 1/109 R clari 1/109 I to clari 1/109 I pen

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Takker 2003 Argentina,Czech Republic,Estonia,Finland,France,Germant,Latvia, Poland,South Africa, Ukraine, Uraguay	randomized, double blind, multicenter	12-75, s/s, cx+	clari 500mg ER QD * 5d vs pen 500mg TID *10d	d8-12, 13-20, 40-50 cure: absence or improvement of s/s without need to change drugs failure: continuation or worsening of s/s recurrance: resolved or improved s/s, then worsened	d8-12, 13-20, 40-50 eradicatioon persistence presumed persistence: lack of efficacy or discontinuation without repeat cx eradication w/ reinfection not evaluable	clari vs pen 57%M/43%F vs 59%M/41%F 28.9(12-69) vs 29.9(12-72) white: 89 vs 91% other: 11 vs 9%	same s/s, infection severity	nr,nr,539	177,nr,362 (ITT), 334(PP) 177 not positive cx, 28 more excluded from PP	3d post tx (8-12 or 13-20d) clari vs pen PP cure: 98% vs 94%, p=0.073, (0,8.3) ITT 92 vs 89%, p=0.274 (-3.7,8.5)
Venuta 1998 Italy	multicenter randomized, observer blind	3-14years s/s, + throat cx	clari 7.5mg/kg BID for 10 days vs. azithromycin 10mg/kg *3 days	day 10 cure:complete resolution s/s improvement: incomplete resolution failure: no improvement or worsening	day 17-20 throat cx eradication: -cx micro failure: +cx	only efficacy evaluated pts: clari 97months (48-147), azi 95 months(49-143) 65 M, 72F 136 white, 1 black		492/NR/174	37/NR/137clinical	clari vs azi cure 96.8% vs 95.9% improvement: 1.6% vs. 2.7% cure+improve: 98.4 vs 98.6% failure: 1.6% vs 1.4%, NR similar

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Takker 2003 Argentina,Czech Republic,Estonia,Finland,France,Germant,Latvia, Poland,South Africa, Ukraine, Uraguay	3d post tx (8-12 or 13-20d) clari vs pen PP cure: 89% vs 90%, p=0.722 (-8.2-5.1) ITT 82 vs 83%, p=0.598 (-8.8, 6.8)	NR	study drug-related AE clari vs pen 11% vs 7% abd pain: 3 vs 1% diarrhea: 1 vs 1% dyspepsia: 0 vs 1% nausea: 1 vs 1%	3pts in each group d/c due to AE	PP - 70% drug taken (or 3d if failed) and +cx, and available for f/u ITT: one dose of drug and positive cx 95% S clari, 100% S pen eradication in 3/12 pts wR clari isolate given clari
Venuta 1998 Italy	clari vs azi for patients with clinical evaluability cure 95.2 vs 94.6% failure 4.8 vs 5.4% "Children who did not complete treatment" - never defined cure 8/19 vs 4/5 failure 11/19 vs. 1/5	not reported	clari 1pt abd pain, 2pt diarrhea azi 2 vommitting & diarrhea, 2 diarrhea	0/0	*day 10 only for clinical cure, but high rates then **undefined "compliance with allocated treatment" much higher in azi 76/81 (93.8%) than clari 64/83(77.1%) p=0.005, 16.7% difference (5.68-27.76 95% CI) interesting this is not tolerability related as "both were well tolerated)

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Weippl 1993 Austria,Argentina,Italy	4 center open label randomized	2-12 years s/s, group A Strept culture	azi 10mg/kg qd *3d vs erythromycin ethylsuccinate 30-50mg/kg in 3 divided doses for 10 days	day 10-12, day 28-32 cure: total resolution s/s improve: amelioration Failure: no change Relapse: return of symptoms at either visit	day 10-12, day 28-32 eradication: no org persistance: continued presence reinfection: positive after a negative culture	5.4 (1-12) azi, 5.0 (2-12) ery		NR/NR/93	3/NR/90 evaluable	azi vs ery cure 86% vs 65% improved 9% vs 33% failure/relapse 4% vs 2%, NR
Pediatrics:										
Adam 1996 Germany	Multicenter, randomized, open label	1-17 years, +CX, s/s	ery estolate 40mg/kg/d in 2 divided doses for 5d vs. pen V 30mg/kg/d in 3	1-3d. After therapy completion (so, 6-8d ery and 11-13d pcn) cure: resolution s/s improvement: "considerable"	1-3d post completion and 6 weeks post eradication: negative failure: persistance of same organism	ery vs pcn 7.1 (3-17) vs 7.1 (3-13) 59.2%M/47.1	similar s/s frequency	NR/NR/227	26/1/201 (5 in ery group due to resistance)	ery vs pcn cure: 87.2 vs 98.0, p<0.01 improved: 10.8 vs 0, p<0.01

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Weippl 1993 Austria,Argentina,Italy	azi vs ery eradicated 91% vs 98% persisted 9% vs 2%	lab tests volunteered pt SE	5/46 (11%) azi pts with SE - 4 GI, 1 HA 6/47(13%) ery pts GI	1 ery pt	1 year old included though had to be 2
Pediatrics:					
Adam 1996 Germany	success: 83.3 vs 87.9 failure: 16.7 vs 12.1	not reported	abd pain, nausea, vomiting, or diarrhea: 8.7% (10/115) ery vs 7.1% (8/112) pcn all AE: 9.6% ery vs 8.9% pen	2 ery vs 4 pen w/d dure to AE.	8 of 216 (3.7%) R to ery, 5 pts w/d from clinical analysis for this fact!!!!

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Cohen,2002 France	randomized, multicenter, open label pcn (blinded to azi dose)	2-12, +cx, s/s PP population had to take 80% meds and have sensitive organism, also ITT	azi 10mg/kg qd *3d vs azi 20mg/kg *3d vs 45mg/kg/d pen vk in 3 divided doses * 10d	Day 14 and day 30 cure or improvement: fever gone and s/s imrproved not necessitating further tx failure: lack of improvement or need for new agent	Day 14 success: eradication of organism or isolation of gentically different isolate failure: same isolate persisted Day 30 if success previously: success relapse reinfection	azi 10 vs azi 20 vs pen 5.8 (2.1-11.5) vs 6.3 (2.3-11.4) vs 6.0 (2.1-11.6) 94M/75F vs 88M/77F vs 87M/80F NR	equal s/s ferquency	nr/nr/501	PP 81/nr/420 (19 due to azi R) ITT 32/nr/469 (28 neg cx)	Day 14 PP group azi10 vs azi20 vs pen success: 94.1 vs 100 vs 94.5, p=0.0035 for azi vs azi failure: 5.9% vs 0% vs 5.5% Day 30 PP group azi10 vs azi20 vs pen success: 89.8 vs 94.8 vs 91.5 failure: 10.2% vs 5.2 vs 8.5 Day 14 ITT group azi10 vs azi20 vs pen success: 83.4 vs 91.5 vs 92.8 failure: 16.6 vs 8.5 vs 7.2
Hamill, 1993 UK, ireland	Randomized, non-blinded, multicenter	2-12 years, +cx, s/s	azi 10mg/kg qd *3d vs 125 (<20kg)-250mg pen vk QID* 10d	1-2d post tx, d29-31 f/u cure:disapperance of s/s improve: improvement or partial dissapearance failed: no chhange or worsening relapse: improvement followed by worsening	1-2d post tx, d29-31 f/u eradicated: complete eradication persistance Superinfection: new organism isolated w/ s/s Colonization: new pathogen w/o s/s	azi vs pcn 7.4 (2-12) vs 7.5 (3-12)years 26M/23F vs 25M/22F NR	same baseline	NR, NR, 96	14/NR/85	Day 9-11 azi vs pcn cure: 38/41 (93%) vs 41/44 (93) improved:5 vs 7% relpased: 2% vs 0%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Cohen,2002 France	Day 14 PP group azi10 vs azi20 vs pen eradication: 57.8 vs 94.2 vs 84.2 failure: 42.2 vs 5.8 vs 15.8 Day 30 PP group azi10 vs azi20 vs pen success: 56.8 vs 82.8 vs 81.6 relapse: 40.5 vs 14.8 vs 13.2 re-infection: 2.7 vs 2.5 vs 5.3 Day 14 ITT group azi10 vs azi20 vs pen success: 50 vs 86 vs 82.5 failure: 50 vs 14.0 vs 17.5	daily diary card	treatment related AE: azi10 vs azi20 vs pen 18.3% vs 23% vs 3% "mostly GI"	w/d due to AE: 1 pcn, 7 azi10grp and 6 in azi20grp	19/315 R to azi in azi groups - the reason ITT looks worse due to 9-10 failures added ?
Hamill, 1993 UK, ireland	Day 9-11 azi vs pen eradicated: 95% vs 95% persisted: 5% vs 5%	patient volunteered info	2 (4%) azi pts w/AE, none pen GI 2 azi, 0 pcn	none reported	Susceptibility not reported

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
McCarty 2000 USA	multicenter, randomized, open label	6mos - 12y, +cx, s/s	clari 7.5mg/kg twice daily for 5d vs 13.3mg/kg pen TID for 10d	Post completeion: 5-9d clari or 10-14d pen and 25-32d cure: all s/s resolvedf improvement: improved but not resolved failure: not improved or worse recurrance: improved or resolved, now worsened indeterminate	End of tx d eradicated persistence: same serology presumed persistance: premature d/c due to AE without cx results eradication w/relapse: eradicated with return of same seology eradication w/erinfection: eradication w/ later new serologic organism eradication with colonization: eradication with organism return and no sx not evaluable: did not meet eligibility	clari vs pen 88.9Mo (12-155) vs 92.8mo (11-153) 47%M/53F vs 43%M/57%F white: 93% vs 92% black: 3% vs 4% asian:<1% vs <1% other: 4 vs 4%	same s/s and severity	nr,nr,528	31,nr,497	48h post-tx clari vs pen cure or improved: 97% clari vs 94% pen day25-32 clari vs pen cure or improved: 81% vs 82%
O'Doherty 1996 Ireland, UK, Sweden	multicenter, dbl blind, randomized	2-13y, +cx, s/s	azi 10mg/kg qd *3d vs azi 20mg/kg *3d vs 125 (<20kg)-250mg pen vk QID* 10d	Day 12-14 and 28-30d Cure: disapperance all s/s improvement: partial s/s disappearnce failure: no change or worsening relapse: improvement followed by worsening or reappearance at day 28-30 visit	Day 12-14, day 28-30 eradication persistence: isolation of same serotype recurrance: reappearance at day 28-30 of same serotype after initail clearing	azi 10 vs azi 20 vs pen 71M/95F vs 83M/77F vs 82M/81F 7.7 (2.6-13.0) vs 7.9 (2.9-13.0) vs 7.7 (2.1-12.7)		NR,NR,489	131/NR/358 azi 10 vs azi 20 vs pen 30 vs 36 vs 26 excluded due to no positive cx	Day 12-14 azi 10 vs azi 20 vs pen Cure or improvement: 99% vs 100% vs 97% failure: 1 vs 0 vs 3% Day 28-30 azi 10 vs azi 20 vs pen cure or improvement: 95 vs 95 vs 98% relapse: 6 vs 5 vs 2%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
McCarty 2000 USA	post-tx visit (2d post) clari vs pen eradication: 94% vs 78%, P<0.001 relapse at 25-32d: 42pt vs 33pts	NR	clari vs pen all AE reported: 54% vs 54%	9 clari, 7pen pts d/c AE	removed from study if: cx-, poor improvement at 72h, lab abnormal, AE or noncompliance, patient request 1% R to clari
O'Doherty 1996 Ireland, UK, Sweden	Day 12-14 azi 10 vs azi 20 vs pen eradication: 98% vs 98% vs 92%, p=0.011 (azi vs pen [not specified])	spontaneous report by patients	azi 10 vs azi 20 vs pen d/C due to AE: 5 (5%)vs 11(8%) vs 2 (1%)pts, p<0.025 between pcn and azi (groups not stated) Treatment-related AE: 9 vs 13 vs 5%	none reported	98.3% S azi

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Pacifico 1996 Italy	single center, randomized, blinding not mentioned	3-12y, +cx, s/s	azi 10mg/kg qd *3d vs 50,000IU/d in 2 divided doses for 10d	Day 12-14 and 34-36 success: resolution or "substantial improvement of s/s failure: not improved or worsened recurrance: worsening after initial improvement at day 12-14	Day 12-14 and 34-36 elimination: gone failure: original serotype still present at vists 12-14d recurrance: eradication at day 12-14 with same serotype isolated at day 34-36 re-infection: eradication at day 12-14, with new serotype at 34-36d	azi vs pcn Age:6.7 (3-12) vs 6.9 (3-12) 47.3%M/52.6%F vs 50/50% NR	same s/s	NR, NR, 183	29/4/154 14pts in azi group not evaluable b/c azi R patients excluded from efficacy	Day 12-14 azi vs pen success: 65/76 vs 73/78 failure: 11/76 vs 5/78 Day 34-36 success: 57/65 vs 71/73 recurrance: 8/65 vs 2/73 Overall success (both visits): 57/76 vs 71/78, p<0.05
Schaad 1996 Switzerland	open label, multicenter	6mos to 14y, ,s/s, +cx	azi 10mg/kg qd *3d vs 56 (100,000IU) mg/kg/d in 3 divided doses for 10d	day 10-14 and 20-30 cure: disappearnce of all s/s improvement: improvement of s/s failure: no change or worsening relapse: improvement or dissaperance followed by worsening or reappearance		azi vs pen age: 7.1(1.5-12.4) vs 6.9 (1.9-13.9) 82M/88F vs 89M/84F NR	azi group with statistical hifger severity score: 14.1 vs 13.5, p=0.047 (scale was 0-3 severity score added for 6 s/s) unlikely clinically significant	nr,nr,343	23/nr/320 21 w/o + cx	All time point response azi vs pen cure: 83% vs 82% improvement:9 vs 7% relaspe: 4 vs 8% undetermined: 1 vs 0%

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Pacifico 1996 Italy	Day 12-14 azi vs pcn elimination: 51/76 vs 71/78 failure: 24/76 vs 7/78 reinfection: 1/76 vs 0/78 Day 34-36 azi vs pen elimination: 38/51 vs 65/71 recurrance: 11/51 vs 4/71 reinfection: 2/51 vs 2/71 overall success (both visits, recurrance considered failure): 38/76 vs 65/78, p<0.0001	not reported	azi vs pen Overall AE: 8/93 vs 5/90 diarrhea: 5/93 vs 2/90 abd pain: 1/93 vs 0/90 nausea: 1/93 vs 0/93 vomitting: 0/93 vs 2/90	none reported	179 GABHS: 17.3% R to azi 14pts w/R azi isolate exclueded from clinical analysis!!
Schaad 1996 Switzerland	Day 10-12 azi vs pen eradication: 65% vs 82%	NR	Treatment related AE: azi vs pen 23 (14%) vs 16 (9%)	1 pt each group d/c due to AE	100% sensitive to both drugs

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Schaad 2002 Switzerland	randomized, multicenter, open label	2-12Y, s/s, cx+	azi 10mg/kg qd *3d vs 56 (100,000IU) mg/kg/d in 3 divided doses for 10d	Day 14, 28 cure, improvement, failure, relapse	Day 14, 28 eradication: - at day 14 relapse: +cx after this time	numbers NR: stated similar gender, age	stated no differences s/s	nr,nr,292	23,nr,269 cx neg in 6 pts, otheres protocol violation, etc	Day 14 azi vs pen cure: 77 vs 85% improvement: 18%vs12% (success): 95% vs 97% no change: 0 vs 0 worsening:1 vs 0% relapse: 4 vs 3% Day 28: cure: 79 vs 89% improve: 15% vs 6% (success): 94 vs 95% no change: 1 vs 0% worsening: 1 vs 0% relpase: 4 vs 5%
Still 1993 USA	multicenter, randmonized, single blind (investigator)	6mos to 12y, s/s, +cx	clari 7.5mg/kg twice daily for 10d vs 13.3mg/kg pen TID for 10d	Day 4-6 post therapy end and 19-25days post treatment cure: s/s resolved improvement: improved but not S/s resolved recurrance: s/s worsened or recurred indeterminate	Day 4-6 post therapy cure: eradicated failure: identical serologic organism relapse: eradicated, reappeared d19-25 indeterminate	all 7.4 (1-16) 264M/242F 400 caucasian 79 black 2 Asian 25other same groups	s/s same	nr,nr,506	nr,4,367 35 neg cx or resistat (even group totals) 30 from single site problem	clari vs pen cure: 86% vs 80% improved: 10 vs 14% success: 96 vs 94% failed: 4 vs 6% recurrance: 8 vs 7% all NS

Evidence table 9. Summary of pharyngitis trials

Author Year Country Trial Name (Quality	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Schaad 2002 Switzerland	Day 14 azi vs pcn eradication: 38% vs 81%, p<0.001 Day 28: azi vs pen 31 vs 68%, p<0.001	NR	treatment related: azi vs pen 6% vs 8%	1 azi, 5 pcn d/c due to AE	In azi group: 93% S azi, 5.5%I, 1.5%R
Still 1993 USA	clari vs pen eradicated: 92 vs 81%, p=0.004 failed: 8 vs 19% relapse: 7 vs 10% reinfected: 1.8 vs 2.5%	NR	all AE clari vs pen 52 vs 46%	clari vs pen (10pts)4% vs (4pts)2% d/c from study due to AE GI: 14% vs 5%, p<=0.001 adb pain: 16pts vs 3pts diarrhea: 14 vs 5pts vomitting: 13 vs 3pts	d/c from study if R to drug 465/471 S clari, 6 I clari 418/471 S pen, 45 I, 8 R to pen **unheardof R to pen!

Evidence table 10. Quality assessment of pharyngitis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential /high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Adam 1996	NR	NR	y	y	n	n	n	y,NR,y,NR	n	y	y	fair
Bachand 1991	NR	na	y	y	y	y	y	y,n,y,n	n	n	y	fair
Cohen 2002	y	NR	y	y	n	n	n	y,NR,NR,NR	n	y	y	fair
Hamill 1993	NR	NR	y	y	NR	NR	NR	y,NR,NR,NR	n	n	y	fair
Hooten 1991	y	na	y	y	n	n	n	y,n,y,n	y	n	y	fair
Kaplan 2001	NR	NR	yes	yes	y	NR	no	yes,NR,yes,NR	no	no	yes	fair
Levenstein 1991	NR	NR	y	y	y	y	y	y,n,y,n	y	n	y	fair
McCarty 2000	NR	na	y	y	n	n	n	y,n,y,n	n	n	y	fair
O'Doherty 1996	NR	NR	y	y	y	y	y	y,NR,y,NR	n	n	y	fair
Pacifico 1996	y	NR	y	y	NR	NR	NR	y,NR,y,NR	n	n	y	fair
Portier 2002	NR	na	y	y	n	n	n	y,n,y,n	n	y	y	fair
Roord 1996	NR	NR	y	y	n	n	n	y,NR,NR.NR	n	n	y	fair
Scaglione 1990	yes	NR	yes	yes	no	no	no	yes,NR,NR,NR	no	no	unable to dtermine	fair
Schaad 1996	y	na	y	y	n	n	n	y,NR,y,NR	n	n	y	fair
Schaad 2002	NR	na	y	y	n	n	n	y,NR,NR,NR	n	n	y	fair
Schrock 1992	NR	NR	y	y	y	y	n	y,n,y,n	n	n	y	fair
Soepandi 1998	y	NR	y	y	n	n	n	n,n,n,n	n	n	y	poor
Stein 1991	y	NR	y	y	y	y	y	y,n,y,n	n	n	y	fair
Still 1993	NR	na	y	y	y	y	n	y,n,y,n	y	n	y	fair
Takker 2003	NR	NR	y	y	y	y	y	y,n,y,n	n	y	y	fair/good
Venuta 1998	NR	NR	yes	yes	y	y	no	y,NR,y,n	no	no	n	fair
Weippl 1993	NR	NR	yes	yes	no	n	no	y,NR,NR,NR	no	no	yes	fair

Evidence table 10. Quality assessment of pharyngitis trials

Author, Year Country	Number screened/eligible/eNRolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Adam 1996				nt	y	Infectopharm Arzneimittel GmbH, Germany	
Bachand 1991						Abbott person as sole author	
Cohen 2002				NR	y	Pfizer	
Hamill 1993				NR	y	NR	
Hooten 1991						Pfizer	
Kaplan 2001			none	NR		Abbott labortatories	
Levenstein 1991						NR	
McCarty 2000						NR	
O'Doherty 1996				NR	y	NR	
Pacifico 1996				NR	y	Italian National Research Council	
Portier 2002						Abbott	
Roord 1996				NR		Pfizer	
Scaglione 1990			none	NR	?	NR	
Schaad 1996				NR		NR, Pfizer author	
Schaad 2002						NR	
Schrock 1992						Abbott	
Soepandi 1998						NR	
Stein 1991						NR	
Still 1993						Abbott	
Takker 2003						Abbott	
Venuta 1998			none	NR		NR	
Weippl 1993			none	NR		NR	

Author, Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Method of Outcome Assessment and Timing of Assessment	Age Gender Ethnicity
Dunne, M., 2000 USA, Brazil, Argentina, Chile, The Netherlands	RCT, double-blind, double-dummy Multicenter	Patients were considered if they had local blood culture positive for MAC within the previous 2 months and if they were infected with HIV, were >13 years old, were expected to survive at least 2 months, had not received therapy for treatment of MAC since the positive culture, had ALT and AST <5 times the upper limits of normal, a SCr of <3.0 mg/dL and a neutrophil count >500 cells/mm3 Patients were excluded if they had a hypersensitivity to macrolides, were pregnant or lactating, were unable to take oral medications, had been previously treated for MAC, or had a condition likely to interfere with drug absorption.	azi 250 mg once daily azi 600 mg once daily clari 500 mg twice daily	ethambutol 800 mg or 1200 mg (weight based) once daily	primary endpoint was culture sterilization - 2 consecutive negative blood cultures for MAC at week 24	secondary endpoints include: time to sterilization, change from baseline in level of mycobacteremia, durability of sterilization, mortality, clinical response as judged by the investigator, change in QOL, and patient tolerance for each regimen	Gender female - 6/65 azi 250, 14/88 azi 600, 13/86 clari male - 59/65 azi 250, 74/88 azi 600, 73/86 clari Mean age - 36 azi 250, 38 azi 600, 37 clari Ethnicity not reported
Ruf, B., 1992 Germany	RCT, double-blind, placebo controlled Single-center	HIV infected patients with clinical s/sx consistent with MAC infection, ther were no s/sx suggestive of other infections.	clari 1000 mg twice daily placebo	INH 300 mg once daily, eth 25 mg/kg once daily, and clofazimine 300 mg once daily	Negative blood culture at end of first phase week 6	NR	Gender - 5 male clari, 4 male placebo Mean Age - 35.2 clari, 38.3 placebo Age Range - 30-38 clari, 25-48 placebo ethnicity not reported
Ward, T., 1998 USA	RCT Multicenter	HIV-1 seropositive patients with a blood culture positive for MAC within 2 weeks, and were at least 18 years old. Patients were excluded if they had received azithromycin, clarithromycin, or ethambutol within 4 weeks before enrollment, had hypersensitivity to any of the study agents, had other concurrent mycobacterial disease such as tuberculosis, had a life expectancy estimated to be <16 weeks, or were unable to take or comply with the oral study regimen.	azi 600 mg once dialy clari 500 mg twice daily	ethambutol 800 mg or 1200 mg (weight based) once daily	Sterilization at week 16	NR	NR

Author, Year Country Trial Name	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow up/ analyzed	Clinical Cure	Mortality	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events
Dunne, M., 2000 USA, Brazil, Argentina, Chile, The Netherlands	subjects in clari and azi 600 groups were more likely to receive prior MAC prophylazis than the azi 250 group	NS not reported / NE not reported / 246 randomized - 239 received therapy	number withdrawn not reported / number lost to fu not reported / 127 analyzed (mITT included only patients with positive culture at time of randomization - 68 azi 600, 57 clari)	Week 24 sterilization - 31/68 (46%) azi 600, 32/57 (56%) clari (95% CI -28-7) p=0.24 Relapse 1 culture - 6/36 (17%) azi 600, 3/34 (9%) clari Hazard ratio 2.0 (95%CI 0.5-8.1) Last follow-up sterilization - 36/68 (53%) azi 600, 34/57 (60%) clari (95%CI -24-11) p=0.24 HR 0.8(95%CI 0.5-1.2) relapse 2 cultures - 4/36 (11%) azi 600, 4/34 (12%) clari HR 1.0 (95%CI 0.2-3.9) p=.95	Week 24 - 16/68 (24%) azi 600, 15/57 (26%) clari (95%CI -18-13) p=0.72 Last follow-up - 47/68 (69%) azi 600, 36/57 (63%) clari HR 1.1(95%CI 0.7-1.7) p=0.73	NR	63% of azi 600 patients had AEs 66% of clari patients had AEs	13 patients withdrew due to AEs (8 azi 600, 5 clari)
Ruf, B., 1992 Germany	CD4 count ranged from 31-143, s/sx reported was similar for all patients	NS not reported / ne not reported / 16 enrolled	7 excluded from analysis / 0 lost to fu / 9 analyzed	blood culture negative week 6 4/4 clari, 2/4 placebo, one patient was unblinded at week 4 due to declining health and switched from placebo to clari, he also had negative cultures by week 6	NR	NR	NR	NR
Ward, T., 1998 USA	all baseline characteristics evaluated were similar among the 2 groups, no statistically significant differences were found	NS not reported / ne not reported / 59 enrolled	22 excluded from analysis / 0 lost to fu / 37 analyzed	sterilization at final study visit 37.5% azi, 85.7% clari p=0.007 sterilization at week 16 - p=0.028 estimated median time to clearance of bacteremia 4.38 weeks clari, >16 weeks azi p=0.0018 ITT of 59 enrolled patients sterilization at week 16 - 45.5% azi, 94.4% clari p=0.011	NR	NR	7/24 azi patients reported AEs 10/35 clari patients reported AEs nausea and gi intolerance most frequently reported	2/24 azi, 3/35 clari discontinued due to AEs

Evidence table 11. Summary of *Mycobacterium avium* complex (MAC) trials

Author, Year Country Trial Name	**Comments**
Dunne, M., 2000 USA, Brazil, Argentina, Chile, The Netherlands	An interim analysis was conducted 1/2 way through the study, at that time the azi 250 arm was closed due to lower sterilization rates compared to azi 600 and clari, and higher proportion of deaths. Mean duration of treatment was 86 days for azi 600 and 69 days for clari. Study did not enroll all needed subjects, predictive value may be effected. Results reporte late follow-up, at week 24 however, patients were switched to open-label therapy at the investigator's discretion but continued to be followed-up every 3 months
Ruf, B., 1992 Germany	the 2 patients whose blood culture is reported as not negative died on week 2 and week 3 respectively. There was no statistical analysis performed on any arm. There was a long-term followup arm, which patients were treated with clari+rifampin for 24 weeks, then clari alone for life-long prophylaxis. These results aren't reported in this table.
Ward, T., 1998 USA	The study originally intended on enrolling 108 patients, however, an interim analysis was performed when half that were enrolled which showed a dignificant difference in study arms in the proportion of patients for whom cultures were negative at 16 weeks (p=0.028). Enrollment was terminated at this time with only 35 clari patients and 24 azi patients.

Evidence table 12. Quality assessment of MAC trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Dunne, M., 2000 USA, Brazil, Argentina, Chile, The Netherlands	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	good
Ruf, B., 1992 Germany	method NR	NR	no demographics reported	yes	NR	yes	yes	no	no	no	yes	poor
Ward, T., 1998 USA	yes	NR	yes	yes	no	no	no	no	no	yes	yes	fair

Evidence table 12. Quality assessment of MAC trials

Author, Year Country	Number screened/eligible/enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Dunne, M., 2000 USA, Brazil, Argentina, Chile, The Netherlands	246 enrolled	Patients were excluded if they had a hypersensitivity to macrolides, were pregnant or lactating, were unable to take oral medications, had been previously treated for MAC, or had a condition likely to interfere with drug absorption.	no	no	yes	Pfizer - industry	good
Ruf, B., 1992 Germany	16 enrolled	NR	no	no	yes	Abbot - industry	poor
Ward, T., 1998 USA	59 enrolled	Patients were excluded if they had received azithromycin, clarithromycin, or ethambutol within 4 weeks before enrollment, had hypersensitivity to any of the study agents, had other concurrent mycobacterial disease such as tuberculosis, had a life expectancy estimated to be <16 weeks, or were unable to take or comply with the oral study regimen.	no	no	yes	Abbot - industry Pfizer - industry	good

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Benson, 2000 USA	RCT, double-blind, placebo-controlled Multicenter	>12 years of age, laboratory evidence of HIV infection, <100 CD4 T lymphocytes/mcL within 90 days of study entry, 2 blood cultures negative for MAC >1 week apart within 30 days of study entry, no s/sx of MAC disease, and a Karnofsky perfomance score >50. Laboratory eligibility requirements included no evidence of actuve pulmonary disease on a chest x-ray, >8 g/dL hemoglobin, ANC >500 cells/mcL, platelet count >50,000 cells/mcL, and AST, bilirubin and SCr levels <5 times, <2.5 times, and <2 times the upper limit of normal, respectively. ART and PCP prophylaxis were encouraged for all patients. Subjects were excluded if they had known or suspected MAC disease, other mycobacterial infection requiring treatment (with the exception of latent TB for which INH chemoprophylaxis was allowed), hypersensitivity to study medications, concurrent use of terfenadine or astemizole, pregnancy or lactation, a history of >4 months of therapy with clarithromycin, azithromycin, or rifabutin in the year prior to study entry, or malabsorption as defined by persistent diarrhea of >6 stools per day for >6 weeks.	clari 500 mg twice daily rifabutin 450 mg once daily (9 months into the study, the dose of rifabutin was decreased to 300 mg once daily due to uveitis) clari 500 mg twice daily + rifabutin 450 mg once daily	antiretroviral medications and PCP prophylaxis	Week 96 development of MAC disease - defined by a single blood culture positive for MAC after randomization or the isolation of MAC from another normally sterile site plus at least 1 s/sx of MAC disease.	
Havlir, D., 1996 USA	RCT, double-blind Multicenter	>18 years of age, documented CD4 cells <100 cells/mm3 within 1 year before study entry, AND >500 cells/mm3, platelets >50000 cells/mm3, SCr and bilirubin concentration less than 3 times the upper limit of normal, AST and ALTconcentrations less than 5 times the upper limit of normal, chst radiograph showing no evidence of active disease, a Karnofshy score aboe 60 for performance status, an expected survival of more than six months, no evidence of an acute opportunisitc infection, and no history of hypersensitivity reactions to clarithromycin, azithromycin, rifampin, or rufabutin. Exlcuded patients included those with documented or suspected mycobacterial infection and pregnant or lactating women.	azi 1200 mg once weekly rifabutin 300 mg once daily azi 1200 mg once weekly + rifabutin 300 mg once daily	patients were independently randomized to receive fluconazole 200 mg once daily or fluconazole 400 mg once weekly to examine fungal prophylaxis concurrently ART was allowed PCP prophylaxis was allowed	Primary endpoint was time to the development of disseminated M. avium complex disease - diagnosed on the basis of positive culture for M. avium complex from blood or another sterile body site blood cultures were done monthly	

Author, Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Clinical Cure	Other outcomes	Method of adverse effects assessment
Benson, 2000 USA	Gender female - 42/398 (11%) clari, 38/391 (10%) rif, 37/389 (10%) clari/rif male - 356/398 (89%) clari, 353/391 (90%) rif, 352/389 (90%) clari/rif Mean age - 37 clari, 39 rif, 39 clari/rif Ethnicity White - 250/398 (63%) clari, 243/391 (62%) rif, 238/389 (61%) clari/rif Black - 94/398 (24%) clari, 110/391 (28%) rif, 96/389 (25%) clari/rif Latino - 45/398 (11%) clari, 32/391 (8%) rif, 50/389 (13%) clari/rif Other - 9/398 (2%) clari, 6/391 (2%) rif, 5/389 (2%) clari/rif	Groups were similar according to CD4 count, IVDU, and current/previous ART	ns not reported / ne not reported / 1216 enrolled	38 were excuded prior to randomization / 0 lost to fu / 1178 analyzed	ITT confirmed MAC - 36 (9%) clari, 59 (15%) rif, 26 (7%) clari/rif time-adjusted event rates per 100 patient-years (95%CI) - 6.3 (4.2-8.3) clari, 10.5 (7.8-13.2) rif, 4.7 (2.9-6.5) clari/rif	reduced risk of MAC - 44% clari (p=.005), 57% clari/rif (p=.0003) compared with rifabutin	not reported
Havlir, D., 1996 USA	Gender male - 96% (n=233) azi, 95% (n=236) rif, 94% (n=224) azi/rif Mean age - 38.2 azi, 38.0 rif, 38.5 azi/rif Ethnicity White - 60% (n=233) azi, 60% (n=236) rif, 61% (n=224) azi/rif Black - 23% (n=233) azi, 19% (n=236) rif, 21% (n=224) azi/rif Hispanic - 15% (n=233) azi, 15% (n=236) rif, 12% (n=224) azi/rif Asian - 0% (n=233) azi, 0% (n=236) rif, 1% (n=224) azi/rif Other - 2% (n=233) azi, 6% (n=236) rif, 5% (n=224) azi/rif	medican CD4 count was higher in combination group - 36 azi, 38 rif, 45 azi/rif	ns not reported / ne not reported / 723 enrolled	693 analyzed in ITT,	ITT incidence of disseminated M. avium comples - 13.9% (31/223) azi, 23.3% (52/223) rif, 8.3% (18/218) azi/rif On-treatment incidence of disseminated MAC - 8.8% (18/204) azi, 11.8% (24/204) rif, and 2.5% (5/199) azi/rif The risk of MAC for patients taking azi was 47% lower (hazard ratio, 0.53; p=0.008) than those taking rif Risk of MAC infection according to treatment group defined as hazar ratio (95%CI) azi vs rif - 0.63 (0.33-1.21) OT, 0.53 (0.34-0.85) ITT azi/rif vs rif - 0.17 (0.06-0.46) OT, 0.28 (0.16-0.49) ITT azi/rif vs azi - 0.27 (0.10-0.74) OT, 0.53 (0.29-0.95) ITT		not reported

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Benson, 2000 USA	GI effects most frequently reported grade 3 or higher nausea and vomiting - 2.5% clari, 3.6% rif, 4/6% clari/rif grade 3 or higher diarrhea - 4.3% clari, 6.7% rif, 4.6% clari/rif uveitis - 42 (3.6%) overall - 33 (78.6%) clari/rif, 7(16.7%) rif, 2 (4.7%) clari	70 patients discontinued due to treatment-limiting AEs, and 184 patients voluntarily discontinued due to toxicity severity less than grade 3	
Havlir, D., 1996 USA	Percentage of patients who reported AEs 88% azi, 90% azi/rif, 76% rif D/C de to GI symptoms - 8% azi, 8% rif, 9% azi/rif Cumulative risk of discontinuation attributed to drug toxicity was higher in the azi/rif group than the azi group (hazard ratio, 1.67; CI 1.10-2.60; p=0.03) GI effects % of patients abdominal pain - 36% azi, 18% rif, 35% azi/rif diarrhea - 56% azi, 26% rif, 58% azi/rif nausea - 37% azi, 25% rif, 36% azi/rif vomiting - 12% azi, 9% rif, 10% azi/rif Statisically significant differences: sig more AEs in azi/rif group than rif and in the azi group than rif; sig higher proportion of GI toxi effects in azi/rif group than fir and the azi group than rif; sig higher proportion of dose-limiting toxic effect in azi/rif group than azi group	dose limiting AEs (% of patients - 13% azi, 16% rif, 23% azi/rif number withrawan unclear	

Evidence table 13. Summary of MAC prophylaxis trials

Author, Year Country Trial Name (Quality Score)	Study Design Setting	Eligibility criteria	Interventions	Allowed other medications/ interventions	Method of Outcome Assessment and Timing of Assessment	Method of Outcome Assessment and Timing of Assessment - Microbiologic Cure
Oldfield, E., 1998 USA	RCT, double-blind, placebo-controlled Multicenter	Men and nonpregnant women who were HIV-seropositive and 18 years of age or older. CD4 count <100 cells/mm3 within the preceding 12 months. 2 blood specimens for MAC cultures were obtained, one at eh screening visit and one at 3-5 weeks after the baseline visit Exclusions include positive blood culture for MAC at screening or baseline, symptoms suggestive of MAC infection, history of MAC infection, or known or suspected TB infection, subjects treated in the 4 weeks before enrollment with any putative therapy for MAC infection or who had a known hypersensitivity to macrolides were also excluded. AST, ALT, alk phos > 5 times the upper limit of normal, a total bilirubin of >2.5 mg/dL or a SCr >2.5 mg/dL or a neutrophil count of <0.50x10(9) were also excluded	azi 1200 mg once weekly placebo once weekly	ART allowed and PCP prophylaxis	blood cultures obtained monthly - primary endpoint was development of MAC infection documented by positive culture form blood or other sterile body site or MAC infection - related symptoms including fever, night sweats, diarrhea, or weight loss unexplained by other etiologies and sufficient to warrant empirical therapy for MAC infection	
Pierce, M., 1996 USA, UK, Germany, France	RCT, double-blind, placebo-controlled Multicenter	Patients >12 years of age who had HIV infection , with a positive enzyme-linked immunosorbent assay confirmed by another method, were elibible for enrollment. Women had to be nonpregnant and nonlactating. Required CD4 count of 100 or less/mm3, at least one negative blood culture for M. aviu clomplex within 30 days before randomization, a Karnofsky performance score of 50 or higher, and a life expectancy of at least six months. Excluded patients include those with history of allergy or hypersensitivity to macrolides, known or suspected infection with M. avium complex, a degree of anemia disproportionate to the severity of the underlying illness, an ANC <500 cells/mm3, hemoglobin <8.0 g/dL, platelet count of <50,000 cells/mm3, SCr greater than twice the upper limit of normal, a total bilirubin level that was more than 2.5 times the upper limit of the normal range, or AST and ALT more than 10 times the upper limit of normal. Patients receiving treatment with terfenadine, astemizole, and antimycobacterially active agent except prophylactic INH, or any investigational agent were also excluded, patients receiving ciprofloxacin r clindamycin for	clari 500 mg twice daily placebo twice daily		incidence of M. avium complex infection - blood cultures performed every month	

Author, Year Country Trial Name (Quality Score)	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to follow-up/ analyzed	Clinical Cure	Other outcomes	Method of adverse effects assessment
Oldfield, E., 1998 USA	Gender male - 84/89 azi, 83/91 placebo female - 5/89 azi, 8/91 placebo Mean age (range) - 41.1 (24-63) azi, 38.2 (24-61) placebo Ethnicity white - 62/89 azi, 59/91 placebo black - 19/89 azi, 17/91 placebo hispanic - 6/89 azi, 9/91 placebo other - 2/89 azi, 6/91 placebo	Median CD4 count similar, use of ART and PCP prophylaxis similar	ns not reported / ne not reported / 182 enrolled	8 patients excluded / 0 lost to fu / 174 analyzed ITT, 174 analyzed in evaluable pt group	Incidence of MAC infection evalualbe pts - 7/85 (8.2%) azi, 20/86 (23.3%) placebo - HR 0.28 (0.12-0.67); p=0.002 ITT-1 (30 days after last dose) - 9/85 (10.6%) azi, 22/89 (24/7%) placebo - HR 0.34 (0.15-0.73); p=0.004 ITT-2 (last follow-up visit) - 13/85 (15.3%) azi, 27/89 (30.3%) - HR 0.41 (0.21-0.79); p=0.006		not reported
Pierce, M., 1996 USA, UK, Germany, France	Gender male - 310/341 clari, 311/341 placebo female - 31/341 clari, 30/341 placebo Mean age (range) - 37.5 (22-66) clari, 37.6 (20-65) placebo Ethnicity white - 290/341 clari, 295/341 placebo nonwhite - 51/341 clari, 46/341 placebo	Groups were similar according to CD4 count.	ns not reported / ne not reported / 682 enrolled	15 patients excluded from analysis / 21lost to fu / 667 included in ITT analysis	Development of M. avium infection - 19/333 (6%) clari, 53/334 (16%) placebo clari versus placebo - hazard ratio 0.31 (95%CI 0.18-0.53) p<0.001 - estimated 69% reduction I the risk of infection		not reported

Author, Year Country Trial Name (Quality Score)	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Oldfield, E., 1998 USA	GI effects most frequently reported - 71/90 (78.9%) azi, 25/91 (27.5%) placebo azi - diarrhea 52.2%, nauses 32.2%, abdominal pain 26.7%,	7 azi patients withdrew due to AEs, 2 placebo patients withdrew due to AEs	The study was terminated early by the sponser in May 1995 on the basis of a preliminary review of data from a seperated study that raised concerns for the placebo group.
Pierce, M., 1996 USA, UK, Germany, France	Patients reporting AEs (percentage) - 91% clari, 88% placebo (p=0.59) taste perversion (11% clari vs 2% placebo p<0.001), rectal disorders (8% clari vs 3% placebo p=0.007), digestive disturbances 28% clari vs 18% placebo p=0.004) The incidence of severe treatment related adverse events was similar in the 2 groups, 7% clari vs 6% placebo. withdrawal due to AEs - 18% clari, 17% placebo	357 patients withdrawn / 92 withdrawn due to adverse effects	The trial was terminated after an interim analysis which showed a significant difference in incidence of MAC infection among the 2 groups

Evidence table 14. Quality assessment of MAC prophylaxis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Benson, C., 2000 USA	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	good
Havlir, D., 1996 USA	NR	NR	yes	yes	NR	yes	yes	no	no	yes	yes	fair
Oldfield, E., 1998 USA	yes	NR	yes	yes	NR	yes	yes	no	no	yes	yes	good

Evidence table 14. Quality assessment of MAC prophylaxis trials

Author, Year Country	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Benson, C., 2000 USA	1216 enrolled	Subjects were excluded if they had known or suspected MAC disease, other mycobacterial infection requiring treatment (with the exception of latent TB for which INH chemoprophylaxis was allowed), hypersensitivity to study medications, concurrent use of terfenadine or astemizole, pregnancy or lactation, a history of >4 months of therapy with clarithromycin, azithromycin, or rifabutin in the year prior to study entry, or malabsorption as defined by persistent diarrhea of >6 stools per day for >6 weeks.	no	no	yes	ACTG, Terry Beirn Community Programs, NIAID/NIH	good
Havlir, D., 1996 USA	723 enrolled	Excluded patients included those with documented or suspected mycobacterial infection and pregnant or lactating women.	no	no	yes	grants from CA Collaborative Treatment Group, Pfizer, and Adria Labs	good
Oldfield, E., 1998 USA	182 enrolled	Exclusions include positive blood culture for MAC at screening or baseline, symptoms suggestive of MAC infection, history of MAC infection, or known or suspected TB infection, subjects treated in the 4 weeks before enrollment with any putative therapy for MAC infection or who had a known hypersensitivity to macrolides were also excluded. AST, ALT, alk phos > 5 times the upper limit of normal, a total bilirubin of >2.5 mg/dL or a SCr >2.5 mg/dL or a neutrophil count of <0.50x10(9) were also excluded	no	no	no	Pfizer Military Medical Consortium for Applied Retroviral Research	good

Evidence table 14. Quality assessment of MAC prophylaxis trials

Author, Year Country	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Eligibility criteria specified?	Outcome assessors masked?	Care provider masked?	Patient masked?	Reporting of attrition, crossovers, adherence, and contamination	Loss to follow-up: differential/high	Intention-to-treat (ITT) analysis	Post-randomization exclusions	Quality Rating
	Internal Validity											
Benson, C., 2000 USA	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	good
Pierce, M., 1996 USA	yes	yes	yes	yes	yes	yes	yes	no	no	yes	yes	good

Evidence table 14. Quality assessment of MAC prophylaxis trials

Author, Year Country	Number screened/ eligible/ enrolled	Exclusion criteria	Run-in/Washout	Class naïve patients only	Control group standard of care	Funding	Relevance
	External Validity						
Benson, C., 2000 USA	1216 enrolled	Subjects were excluded if they had known or suspected MAC disease, other mycobacterial infection requiring treatment (with the exception of latent TB for which INH chemoprophylaxis was allowed), hypersensitivity to study medications, concurrent use of terfenadine or astemizole, pregnancy or lactation, a history of >4 months of therapy with clarithromycin, azithromycin, or rifabutin in the year prior to study entry, or malabsorption as defined by persistent diarrhea of >6 stools per day for >6 weeks.	no	no	yes	ACTG, Terry Beirn Community Programs, NIAID/NIH	good
Pierce, M., 1996 USA	682 enrolled	Excluded patients include those with history of allergy or hypersensitivity to macrolides, known or suspected infection with M. avium complex, a degree of anemia disproportionate to the severity of the underlying illness, an ANC <500 cells/mm3, hemoglobin <8.0 g/dL, platelet count of <50,000 cells/mm3, SCr greater than twice the upper limit of normal, a total bilirubin level that was more than 2.5 times the upper limit of the normal range, or AST and ALT more than 10 times the upper limit of normal. Patients reveiving treatment with terfenadine, astemizole, and antimycobacterially active agent except prophylactic INH, or any investigational agent were also excluded, patients receiving ciprofloxacin r clindamycin for non-mycobacterial infections were eligible if the duration of treatment was less than 21 days.	no	no	no	Abbott - industry	good

Evidence table 15. Summary of mixed conditions trials

Author Year Country Trial Name	Study Design Setting	Eligibility criteria	Interventions	Method of Clinical Outcome Assessment and Timing of Assessment	Method of Microbiological Outcome Assessment and Timing of Assessment	Age Gender Ethnicity	Other population characteristics	Number screened/ eligible/ enrolled	Number withdrawn/ lost to fu/analyzed	Clinical Cure
Roord, 1996 Netherlands	multicenter, randomized, open label	2-16 years w/ CAP or bronchitis: minimum of 3 sx: cough, tachnpnea, fever >=38, leukocytosis, chest exam w/ rhonchi or rales or consolidation, and/or CXR	azi 10mg/kg QD *3d vs ary40mg/kg/d in 3 divided doses for 10d	day 10-14, day 25-30 Cure: complete remisssion of s/s improvement: amelioration of s/s failure: unchanged or worsening S/s results for CAP/bronchitis not divided	micro, serology eradication colonization: organism not thought to be causing disease indeterminant	azi 4.9y vs 5.6 yr ery azi: 28M/17F, ery 22M/18F	azi 34 CAP/ 11 bronchitis ery 34 CAP, 6 bronchitis	NR/NR/89	4/2/1985	azi vs ery Day 10-14 cure: 31/44 vs 27/40 improvement: 12/44 vs 9/40 failure: 1/44 vs 4/40 Day 25-30 cure: 41/44 vs 33/36 improvement: 1/44 vs 3/36 failure: 0 vs 0 relapse: 2/44 vs 0/36 not reporeted by indication
Soepandi 1998 Indonesia	open-label, randomized, ?single center	>16 years, pneumonia;acute bronchitis and acute exacerbations chronic bronchitis physical exam, c-xray	Azithromycin 500mg QD * 3d vs. clarithromycin 500mg BID for 10d	d10-14 cure: disppearnce of clinical s/s improvement: improvement in or partical disappearance of s/s failure: no change or worsening s/s	d10-14 eradication: eradication or no culturable material (absence of cough) superinfection: new pathogen that requires treatment persistence: persistance of all pathogens not evauable: no organism isolated	azi vs clari 9M/8F vs 13M/4F 36.11 yr vs 37.88yr NR	azi vs clari Pneumonia pts #: 7 vs 9 Acute bronchitis: 6 vs 4 pt AECB: 4 vs 4pts	nr,nr,40	6,nr,34 (5 azi, 1 clari pt excluded - no explanations)	azi vs clari cure: 93.33 vs 58.82% improved: 6.66 vs 41.17% small sample size not reported by indication

Evidence table 15. Summary of mixed conditions trials

Author Year Country Trial Name	Microbiological Cure	Method of adverse effects assessment	Adverse Effects Reported	Total withdrawals; withdrawals due to adverse events	Comments
Roord, 1996 Netherlands	Not reported, stated no difference in eradication rates	method NR	azi vs ery total pts w/AE: 12/45pt vs 6/40pt diarrhea: 4/45 vs 4/40 vomiting: 7/45 vs 1/40 nausea: 4/45 vs 0/40 abd discomfort: 2/45 vs 3/40	no w/d reported	had to take all drug for evaluation (unless d/c due to AE or failure) Included b/c majority CAP (80%) 64pts vs 17pts bronchitis Hflu (19pts) and spneumo(11pts) most common, serology + in 16pts all isoltes S to azi; of H.flu: 4 S ery, 11 I ery, 4 R ery
Soepandi 1998 Indonesia	d10-14 azi vs clari eradicated: (16 pts)94.12 vs 70.59% persistant: 5.88 vs 17.65% superinfection: 0 vs 5.88% not evaluable: 0 vs 5.88% very small sample sizes, stats NR	NR	None reported	None	52 organisms isolated azi:65% S, 31%I, 3.8%R clari: 42%S, 10%I, 49% R

Evidence table 16. Adverse events reported with macrolide use

Study Author Year	Total N enrolled	Mean Age Gender M/F	Side Effects macrolide vs comparator total side effects #/# (%) vs #/# (%) GI side effects #/# (%) vs #/# (%) separate GI type AE if available
CAP studies			
Gotfried, M.H., 2002	299	F : 64/156 vs 70/143 M : 92/156 vs 73/143 MA : 49.0 vs 51.2	clarithromycin vs levofloxacin n=156 vs n=143 total SE: 26% vs 20% diarrhea: 6% vs 6% headache: 3% vs 4% nausea: 3% vs 3%
Hoeffken, G., 2001	678	F : 87/229 vs 87/224 vs 84/222 M : 142/229 vs 137/224 vs 138/222 MA : 48.4 vs 48.0 vs 48.2	moxifoxacin(400) vs moxi(200) vs clarithromycin n=177 vs n=180 vs n=174 diarrhea: (19) 8.5% vs (13) 5.7% vs (8) 3.6% nausea: (9) 4.0% vs (9) 3.9% vs (8) 3.6% abd pain: (8) 3.6% vs (9) 3.9% vs (3) 1.4% nausea & vomiting: (5) .9% vs (2) .9% vs (5) 2.3% vomiting: (5) 2.2% vs (3) 1.3% vs (4) 1.8%
Lode, H., 2004	286	F : 61/141 vs 66/145 M : 80/141 vs 79/145 MA : 48.9 vs 50.0	gatifloxacin clarithromycin n= 141 vs n=145 total GI: (16) 11.4% vs (10) 7% nausea: (8) 5.7% vs (2) 1.4% diarrhea: (6) 4.3% vs (3) 2.1% vomiting: (2) 1.4% vs (2) 1.4% loose stools: 0 vs (3) 2.1%
Mathers Dunbar, L., 2004	493	F : 102/204 vs 109/212 M : 102/204 vs 103/212 MA : 43.8 vs 46.4	telithromycin vs clarithromycin total AE : 126/221 (57) vs 109/222 (49.1) total GI : 85/143 (59.4) vs 55.81 (48.4) diarrhea : 28 vs 16 nausea : 19 vs 11 vomiting : 0 vs 3
Rahav, G., 2004	123	F/M ratio : 1.48 vs 0.64 MA : 50 vs 51	azithromycin vs comparative treat. N=62 vs n=46 total SE: NR nausea: (3) 4.8% vs 0
Ramirez, J., 1999	342	F : 69/167 vs 90/175 M : 98/167 vs 85/175 MA : 51 vs 51.3	sparfloxacin vs clarithromycin n=167 vs n=175 total SE: (13) 7.8% vs (7) 4.0% total GI: (19) 11.4% vs (24) 15.4% abd pain: 0 vs (4) 2.3% diarrhea: (6) 3.6% vs (13) 7.4% dyspepsia: (2) 1.2% vs (4) 2.3% nausea: (6) 3.6% vs (12) 6.9% vomiting: (5) 3.0% vs (3) 1.7%
Sokol, W.N., Jr., 2002	176	F : 47/90 vs 45/86 M : 43/90 vs 41/86 MA : 47.6 vs 47.3	clarithromycin vs trovafloxacin diarrhea: (4/90) 4% vs NR nausea: (3/90) 3% vs (4/86) 5% vomiting: NR vs (3/86) 3% constipation: NR vs (3/86) 3%
Sinusitis studies			
Adelglass, J. 1998	216	levofloxacin vs clarithromycin n=101 vs n=109 M.A. (41.1) vs (38.8) F: (42) 41.6% vs (27(30.3% M: (59) 58.4% vs (63) 69.7%	levofloxacin vs clarithromycin n=107 vs n= 108 total SE: (22) 20.3% vs (43) 39.7% total GI: (11) 10.2% vs (19) 17.6% abd pain: (2) 1.9% vs (4) 3.7% nausea: (6) 5.6% vs (7) 6.5% diarrhea: (1) .9% vs (6) 5.6% constipation: (1) .9% vs 0 flatulence: (1) .9% vs (1) .9% vomiting: 0 vs (1) .9%

Evidence table 16. Adverse events reported with macrolide use

Study Author Year	**Total N enrolled**	**Mean Age Gender M/F**	**Side Effects macrolide vs comparator total side effects #/# (%) vs #/# (%) GI side effects #/# (%) vs #/# (%) separate GI type AE if available**
HeNRy, D.C., 1999	504	no statistically significant difference in demographic characteristics between treatment groups with respect to age, sex. MA : NR F / M : NR	sparfloxacin vs clarithromycin n=252 vs n=252 total SE: (60) 23.8% vs (68) 27% total GI: (33) 13.2% vs (41) 16.3% diarrhea: (12) 4.8% vs (16) 6.3% nausea: (12) 4.8% vs (12) 4.8% abd pain: (4) 1.6% vs (9) 3.6% flatulence: (5) 20% vs (4) 1/6%
Husfeldt, P. 1993	319	F : 105/136 vs 104/144 M : 31/136 vs 40/144 MA : 38 vs 40	oflaxacin vs erythromycin (18/155) vs (32/164) total SE: (27) vs (45) total GI: (19) vs (41) diarrhea: (4) vs (7) nausea: (6) vs (13) flatulence: (1) vs 0 vomiting: (2) vs (2) gastralgia: (3) vs (11) obstipation: (1) vs 0 dyopepsia: (2) vs (7)
Lasko, B. 1998	236	F : 55.5/119 vs 58.1/117 M : 44.4/119 vs 41/9/117 MA 40.4 vs 39.9	levofloxacin vs clarithromycin n=119 vs n=117 total SE: (27/59) 22.7% vs (46/93) 39.3% total GI: (20/40) 16.7% vs (39/66) 33.3%
Stefansson, P. 1998	370	F : 100/185 vs 113/185 M : 85/185 vs 72/185 MA : 36.5 vs 37.2	cefuroxime axetil vs clarithromycin total SE: (17/185) 9% vs (18/185) 10% total GI: (13) vs (8)
AECB, ABECB trials			
Aldons - 1991	125	clarithromycin vs ampicillin F: 27/60 vs 28/65 M: 33/60 vs 37/65 MA: 60.3 vs 58.0	clari vs ampi total AE: 7 (11.7%) vs 3 (4.6%) total GI: 6 (10%) vs 1 (1.5%) nausea: 4 (6.6%) vs 0 vomiting: 2 (3.3%) vs 0 abd. pain: 1 (1.7%) vs 1 (1.5%)
Amsden - 2003	1235	azithromycin vs levofloxacin F: 54/118 vs 65/117 M: 64/118 vs 52/117 MA: 58.6 vs 56.5	azi vs levo total AE: NR total GI: NR diarrhea: 8.5% vs 4.3% nausea: 0.8% vs 6%
Anzueto - 1997	743	ciprofloxacin vs clarithromycin F: 177/349 vs 192/363 M: 172/349 vs 171/363 MA: 62.6 vs 62.8 (n=369 vs n=374)	cipro vs clari total AE : 74 (20%) vs 62 (17%) total GI : 37 (10%) vs 21 (6%) diarrhea: 9 (2%) vs 6 (2%) nausea : 13 (4%) vs 7 (2%) vomiting : 7(2%) vs 5 (1%)
Anzueto - 2001	287	clarithromycin vs amoxicillin F : 68/142 vs 68 / 145 M : 74/ 142 vs 77 / 145 MA : 58.3 vs 57.2	clari vs amo total AE :30 vs 34 total GI : 19 vs 22 diarrhea: 12 vs 18 nausea : 7 vs 4
Bachand - 1991	128	clarithromycin vs penicillin V F : 41/65 vs 48/63 M : 24/65 vs 15/63 MA : NR	clari vs pen total AE : 28 (43.1%) vs 17 (27.0%) total GI : 19 (29.2%) vs 8 (12.7%)
Balmes - 1991	110	azithromycin vs amoxicillin F : 22/52 vs 19/58 M : 30/52 vs 39/58 MA : 57.9 vs 60.7	azi vs amo total SE : 3 (6%) vs 7 (12%) total GI : NR
Beghi - 1995	142	azithromycin vs amoxicillin / clavulanic F : 26/69 vs 16/73 M : 43/69 vs 57/73 MA : 65.7 vs 65.9	azi vs amo total SE : NR diarrhea: 0 vs 1

Evidence table 16. Adverse events reported with macrolide use

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Biebuyck - 1996	759	azithromycin vs co-amoxiclav F : 230/501 vs 106/258 M : 268/501 vs 152/258 MA : 45 vs 44	azi vs co-amo total AE : 98/501 (14%) vs 72/258 (21.3%) total GI : (71.4%) vs (80.6%)
Chodosh - 1998	376	ciproloxacin vs clarithromycin F : 16/107 (15%) vs 28/104 (27%) M : 91/107 (85%) vs 76/104 (73%) MA : 61.4 vs 61.7	cipro vs clari total AE : 60 (32%) vs 71 (38%) total GI : NR
Chodosh - 2000	936	moxifoxacin(5day) vs moxi(10day) vs clarithromycin F : 143/312 (46) vs 142/302 (47) vs 154/312 (49) M : 169/312 (54) vs 160/302 (53) vs 158/312 951) MA : 56.9 vs 56.2 vs 55.5	moxi 5 vs moxi 10 vs clari total AE : 26% vs 30% vs 33% total GI : 41/312 (13) vs 53/302 (19) vs 54/312 (18) diarrhea : (5) vs (6) vs (5) nausea : (4) vs (8) vs (7) vomiting : (<1) vs (3) vs (3) dyspepsia : (2) vs (<1) vs (<1) flatulence : (1) vs (<1) vs (18)
Dark - 1991	546	azithromycin vs cefaclor F : 178/367 vs 92/179 M : 189/367 vs 87/179 MA : 51.4 vs 51.0	azi vs cefa total AE : 79/367(21.5%) vs 22/179(18.4%) total GI : (65.5%) vs (61.0%)
De Cock - 1988	198	amoxicillin vs erythromycin F : 53/97 vs 46/101 M : 44/97 vs 55/101 MA : total 61.75	amox vs ery total AE : 19 (1.5) vs 47 (1.8) total GI : 5 vs 19 nausea : 2 (1.5) vs 7 (1.7) vomiting : 1 (2) vs 9 (2.7) diarrhea : 2 (1.5) vs 3 (1.3)
DeAbate - 2000	567	moxifloxacin vs azithromycin F : 101/221 (46%) vs 108/243 (44%) M : 120/221 (54%) vs 135/243 (56%) MA : 53.9 vs 54.5	moxi vs azi total AE : 61/283 (22%) vs 49/284 (17%) total GI : 33/283 (12%) 35/284 (12%) nausea : 15 (5%) vs 9 (3%) diarrhea : 13 (5%) vs 19 (7%) abd. Pain : 5 (2%) vs 7 (2%)
Fogarty - 2005	1245	telithromycin vs comparators F : 290/612 (47.4%) vs 280/633 (44.2%) M : 322/612 (52.6%) vs 353/633 (55.8%) MA : 57.7 vs 59.0	teli vs comp total AE : 248/609 vs 301/626 total GI : NR diarrhea : 39/609 (6.4%) vs 59/626 (9.4%) nausea : 29/609 (4.8%) vs 28/6266 (4..5%)
Fong - 1995	197	clarithromycin vs cefaclor F : 51/95 (53.6) vs 47/102 (46) M : 44/95 (46.3) vs 55/102 (53.9) MA : 54.7 vs 51.5	clari vs cefac total AE : 45 vs 32 total GI : 18 vs 21 abd pain : 7 vs 4 diarrhea : 6 vs 4 nausea : 5 vs 6
Fraschini - 1990	103	clarithromycin vs josamycin F/M : NR MA : NR	clari vs josa total AE : (5.8%) vs (7.8%) nausea : 0/52 vs 1/51 diarrhea : 1/52 vs 0/ 51
Gotfried - 2001	527	gatifloxacin(5 day) vs gati (7day)clarithromycin F : 73/174(42%) vs 51/175(89%) vs 46/178(81%) M : 101/174(58%) vs 49/175(86%) vs 97/178(97%) MA : 48 vs 49 vs 48	gati (5) vs gati (7) vs clari total AE : NR total GI : NR diarrhea : (7%) vs (6%) vs (6%) nausea : (5%) vs (6%) vs (6%)
Gould - 1977	40	penicillin(20) vs erythromycin(20) F/M : NR MA : NR	total AE : NR total GI : NR
Gris - 1996	78	azithromycin vs co-amoxiclav F : 12/41 vs 9/37 M : 29/41 vs 28/37 MA : 60.6 vs 59.3	azi vs co-amo total AE : 8/41 vs 7/37 total GI : 7/41 vs 7/37 diarrhea : 2/41 vs 1/37 oesophagitits : 1/41 vs 0/37 ab. Heptic function : 1/41 vs 2/37 nausea : 2/41 vs 2/37 vomiting : 1/41 vs 2/37

Evidence table 16. Adverse events reported with macrolide use

Study Author Year	Total N enrolled	Mean Age Gender M/F	Side Effects macrolide vs comparator total side effects #/# (%) vs #/# (%) GI side effects #/# (%) vs #/# (%) separate GI type AE if available
Guay - 1992	103	clarithromycin vs ampicillin F : 22/53 vs 23/50 M : 31/53 vs 27/50 MA : 57.5 vs 53.9	clari vs ampi total AE : (15%) vs (20%) total GI : 5 (10%) vs 7 (14%) diarrhea : 3(6%) vs 3 (6%) nausea : 2 (4%) vs 1 (2%) abnormal feces : 0 vs 1 (2%) bloody feces : 0 vs 1 (2%)
Halpern - 2002	428	gemifloxacin vs clarithromycin F : (49.5%) vs (45.1%) M : (50.5%) vs (54.9%) MA : 58 vs 57	gemi vs clari total AE : NR total GI : NR
Hoepelman - 1993	99	azithromycin vs erythromycin F/M : NR MA : NR	azi vs ery total AE : NR total GI : NR
Hoepelman - 1997	197	clarithromycin vs cefaclor F : 51/95 (53.6) vs 47/102 (46) M : 44/95 (46.3) vs 55/102 (53.9) MA : 54.7 vs 51.5	clari vs cefac total AE : 45 vs 32 total GI : 18 vs 21 abd pain : 7 vs 4 diarrhea : 6 vs 4 nausea : 5 vs 6
Hueston - 1991	45	abluterol vs erythromycin F : 9/17 vs 11/17 M : 8/17 vs 6/17 MA : 44.1 vs 33.3	albut vs ery total AE : NR total GI : NR
Khan - 2003	300	cefaclor vs clarithromycin F : 21/144 vs 20/156 M : 115/156 vs 122/156 MA : 53.17 vs 54.19	cefac (n=136) vs clari (n=142) total AE : 28 (18.1%) vs 28 (19.5%) total GI : 9 (6.3%) vs 16 (11.2%) diarrhea : 5 (3.5%) vs 6 (4.2%) abd. Pain : 4 (2.8%) vs 6 (4.2%) flatulence : - vs 2 (1.4%) nausea : - vs 2 (1.4%)
Langan - 1998	684	cefuroxime vs clarithromycin F : 135/140 (40%) vs 142/344 (41%) M : 205/340 (60%) vs 202/344 (59%) MA : 55.9 vs 57.1	cefur vs clari total AE : 68/340 (20%) vs 81/344 (24%) total GI : (9%) vs (8%)
Langan - 1999	805	grepafloxacin vs clarithromycin vs GRE (10 day) F : 13/273 (49%) vs 111/268 (41%) vs 117/261 (45%) M : 140/273 (51%) vs 157/268 (59%) vs 144/261 (55%) MA : 56.8 vs 56.3 vs 57.3	grepa vs clari vs GRE total AE : 10 (4%) vs 13 (5%) vs 13 (5%) total GI : 19 (8%) vs 30 (12%) vs 39 (15%) nausea : 5 (2%) vs 5 (2%) vs 12 (4%) vomiting : 1 (<1%) vs 5 (2%) vs 7 (3%) dirarrhea : 3 (1%) vs 4 (2%) vs 5 (2%) GI discomfort : 0 vs 3 (1%) vs 2 (<1%)
Laurent - 1996	204	azithromycin vs roxithromycin F : 39/104 vs 46/100 M : 65/104 vs 54/100 MA : 58.3 vs 55.9	azi vs roxi total AE : 7 vs 11 total GI : 6 vs 9 abd pain : 3 vs 1 dyspepsia : 1 vs 0 diarrhea : 1 vs 0 nausea : 2 vs 0 gastritis : 0 vs 1 vomiting : 0 vs 3
Lipsky - 1999	298	sparfloxacin vs clarithromycin F : 75/145 (30%) vs 68/153 (44.4%) M : 70/145 (51.7%) vs 85/153 (55.6%) MA : 54.0 vs 58.1	spar vs clari total AE : 38/145 (26.2%) vs 37/153 (24.2%) total GI : NR
Martinot - 2001	250	clarithromycin vs amoxicillin F : 38/127 (30%) vs 53/123 (43%) M : 89/127 (70%) vs 70/123 (57%) MA : 63.6 vs 64.4	clari vs amox total AE : 13% vs 22% total GI : 15% vs 6% diarrhea : 2% vs 10% nausea : 2% vs 3% abd pain : 2% vs 2%
McCarty - 2001	295	cefprozil vs clarithromycin F/M : NR MA : 50 vs 51	cefp vs clari total AE : 27% vs 34% total GI : 14% vs 20% nausea : 7/150 (5%) vs 11/145 (8%) diarrhea : 14/150 (9%) vs 18/145 (12%)

Evidence table 16. Adverse events reported with macrolide use

Study Author Year	Total N enrolled	Mean Age Gender M/F	Side Effects macrolide vs comparator total side effects #/# (%) vs #/# (%) GI side effects #/# (%) vs #/# (%) separate GI type AE if available
Neu - 1993	213	clarithromycin vs cefixime F : 50/103 vs 45/110 M : 53/103 vs 65/110 MA : NR	clari vs cefi total AE : 30/103 vs 25/110 total GI : 15 (15%) vs 16 (15%)
Peugeot - 1991	56	ofloxacin vs erythromycin F/M : NR total MA : 44 90% M	oflo vs ery total AE : 8/28 vs 4/28 total GI : 4/28 vs 2/28
Salzberg - 1993	50	brodimoprin vs erythromycin F : 9/25 vs 8/25 M : 16/25 vs 17/25 MA : 4.1 vs 3.5	brodi vs ery total AE : 3/25 vs 1/25 total GI : NR stomatitis : 1 vs 0 vomiting : 1 vs)
Schouenborg - 2000	239	azithromycin vs pivampicillin F : 49.3% vs 48.% M : 50.7% vs 51.5% MA : 59.4 vs 61.0	azi vs piva total AE : 20/138 (14%) vs 22/98 (22%) total GI : NR diarrhea : 5% vs 11% abd pain : 5% vs 0 nausea : 0 vs 3%
Tewari - 1970	100	erythromycin vs tetracyclin F : 18/50 vs 10/50 M : 32/50 vs 40/50 MA : NR	ery vs tetra total AE : 3 vs 6 nausea and vomiting : 0 vs 4 diarrhea : 0 vs 2 abd discomfort : 2 vs 0
Vagliasindi - 1997	152	flurythromycin vs clarithromycin F : 16/75 vs 18/77 M : 59/75 vs 59/77 MA : 60.12 vs 61.03	flury vs clari total AE : 10 vs 16 total GI : 10% vs 16% nausea : 3 vs 6 diarrhea : 2 vs 3
Wettengel - 1993	408	clarithromycin vs cefaclor F : 86/207 vs 80/201 M : 121/207 vs 121/201 MA : 54.1 vs 53.3	clari vs cefac total AE :12 (5/9%) vs 26 (17.5%) total GI : 7 (3.4%) vs 11 (5.5%) abd pain : 3 (1.4%) vs 1 (0.5%) diarrhea : 2 (1.0%) 4 (2.0%) dyspepsia : - vs 4 (2.0%) nausea and vomiting : 1 (0.5%) vs 2 (1.0%)
Wiesner - 1993	n=297	EA vs doxycycline F : 62 vs 70 M : 86 vs 79 MA : 44.1 vs 41.7	EA vs dox total AE : 20 vs 16 total GI : 12 vs 11
Willey - 1978	72	ampicillin vs erythromycin vs erythromycin + total F : 23 total M : 49 total MA : 57.8	ampi vs ery vs ery+ total AE : 15 vs 4 vs 16 total GI : 11 vs 4 vs 10 nausea : 9 vs 1 vs 7 diarrhea : 2 vs 3 vs 3
Wilson - 1999	750	moxicillin vs clarithromycin F : 131/322 (40.7%) vs 136/327 (41.6%) M : 191/322 (59.3%) vs 191/327 (58.4%) MA : 60.0 vs 60.2	moxi vs clari total AE : 58 (15.4%) vs 65 (17.5%) total GI : 39 (10.3%) vs 38 (10.2%) nausea : 20 (5.3%) vs 15 (4.0%) diarrhea : 11 (2.9%) vs 15 (4.0%) abd pain : 8 (2.1%) vs 8 (2.2%)
Wilson - 2002	712	gemifloxacin vs clarithromycin F : 180/351 (51/3%) vs 161/358 (45.0%) M : 171/351 (48.7%) vs 197/358 (55.0%) MA : 58.7 vs 58.4	gemi vs clari total AE : 66/351 (18.8%) vs 90/358 (25.1%) total GI : NR diarrhea : 18 (5.1%) vs 25 (7.0%)
Ziering - 1998	n=309	ceftibuten vs clarithromycin F : 89/152 vs 82/151 M : 67 vs 71 MA : 48.3 vs 48.9	cefti vs clari total AE : 8/152 vs vs 33/151 total GI : 15/151 vs 6/152
Otitis media			
Ables - 2004	n=304	F / M : NR MA : NR	amoxicillin / clav vs azithromycin total AE : NR total GI : NR
Aronovitz - 1996	169	azithromycin vs amoxicillin / clavulanate F : 33/85 vs 41/84 M : 52/85 vs 43/84 MA : 4.3 vs 3.8	azi vs amox / clav total AE : 3 (3.5%) vs 26 (31.0%) total GI : 3 (3.6%) vs 25 (32.1%) loose stools : 1 (1.2%) vs 9 (10.7%) abd pain : 1 (1.2%) vs 1 (1.2%) diarrhea : 1 (1.2%) vs 15 (17.8%)

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Arrieta - 2003	296	azithromycin vs amoxicillin F : 12.2 vs 13 M : 12.8 vs 12.5 MA : 24.6 vs 25.7	azi vs amox total AE : 55/153 vs 73.147 total GI : 44 vs 59 diarrhea : 30 (19.6%) vs 44 (29.9%) vomiting : 8 (5.2%) vs 12 (8.2%) abd pain : 6 (3.9%) vs 3 (2.0%)
Aspin - 1994	180	clarithromycin vs amoxicillin F: 36/90 (40%) vs 45/90 (50%) M :54/90 (60%) vs 45/90 (50%) M.A. 2.9 vs 3.4	clari vs amoxi total AE : 29/90 vs 46/90 total GI : 32 vs 33 vomiting: (24) 27% vs (19) 21% diarrhea: (8) 9% vs (14) 15%
Cremonesi - 1987	NR	cefatrizine vs erythromycin F / M : NR MA : NR	NR
Dagan - 2000a	138	azithromycin vs cefaclor F : 44% vs 42% M : 56% vs 68% MA : 11.1 vs 12.0	azi vs cefac total AE : (both macrolides) 5 total GI : NR
Dagan - 2000b	238	amoxicillin/clavulanate vs azithromycin F / M : NR MA : 16.2 vs 15.6	amox / clav vs azi total AE : 12/118 (10%) vs 2/120 (2%) total GI : NR vomiting : 10/118 (8%) vs 0/120 (0%)
Dagan - 2001	192	amoxicillin vs azithromycin vs TMP-SMZ F : 7 (24%) vs 14 (34%) vs 22 (45%) M : 22 (76%) vs 27 (66%) vs 27 (55%) MA : 12.8 vs 11.3 vs 8.1	amox vs azi vs TMP total AE : NR total GI : NR
Daniel - 1993	93	F : 45/105 vs 27/50 M : 60/105 vs 27/54 MA : 4.4 vs 4.8	azithromycin vs co-amiclav total AE : 8 vs 2 total GI : NR diarrhea : 1 vs 0 vomiting : 1 vs 0
Dunne - 2003	373	azithromycin vs co-amoxiclav F / M : NR MA : 3.5 vs 3.7	azi vs co-amo total AE : 11% vs 20% total GI : NR diarrhea : 5.9% vs 14.6% vomiting : 2.1% vs 1.1%
Gooch - 1993	379	clarithromycin vs cefaclor F : 95/199 vs 77/180 M : 104/199 vs 103/180 MA NR	clari vs cefac total AE : 30 (15.1%) vs 31 (17.2%) total GI : 19 vs 17 diarrhea : 10 (50%) vs 6 (3.3%) vomiting : 5 (2.5%) vs 9 (5.0%) abd pain : 3 (1.5%) vs 1 (0.6%) gastroentitis : 0 vs 1 (0.6%) nausea : 1 (0.5%) vs 0
Gooch - 1999	334	loracarbef vs clarithromycin F : 88 vs 83 M : 80 vs 83 MA : NR	
Hoberman - 2005	730	amoxicillin / clavulanate vs azithromycin F : 171/367 (46.7%) vs 146/363 (40.2%) M : 196/367 (53.4%) vs 217/363 (59.8%) MA : 15.3 vs 14.9	amox/clav vs azi total AE : 139 (37.9%) vs 128 (35.3%) total GI : NR diarrhea : 21 (5.7%) vs 13 (3.6%)

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Khurana - 1996	527	azithromycin vs amoxicillin-clavulanate F : 126/263 vs 125/263 M : 137/263 vs 138/263 MA : 5.5 vs 5.8	azi vs amox total AE : 19/263 (7.2) vs 45/263 (17.1) total GI : 16/263 (6.1) vs 39/263 (14.8) loose stools : 3 (1.1) vs 4 (1.5) vomiting : 5 (1.9) vs 8 (3.0) abd pain : 4 (1.5) vs 3 (1.1) dyspepsia : 1 (.04 vs 4 (1.5) flatulence : 1 (.4) vs 1 (.4) nausea : 3 (1.1) vs 5 (1.9) diarrhea : 3 (1.1) vs 25 (9.5)
McCarty - 1993	338	clarithromycin vs amoxicillin F : 66/161 vs 76177 M : 95/161 vs 101/177 MA : 3.9 vs 3.8	clari vs amox total AE : 50/161 (31%) vs 74/177 (42%) total GI : NR diarrhea : 12% vs 32%
McLinn - 1996	674	azithromycin vs amoxicillin/clavulanate F / M : NR MA : NR age range 1-15 yrs	azi vs amox/clav total AE : 29/340 vs 117/334 total GI : 27/340 (7.9%) vs 96/334 (28.7%) diarrhea : 8 (2.4%) vs 54 (16.2%) abd pain : 7 (2.0%) vs 15 (4.5%) vomiting : 5 (1.5%) vs 23 (6.9%) nausea : 2 (0.6%) vs 9 (2.7%)
Oguz - 2003	78	azithromycin vs cefaclor F : 21 vs 12 M : 20 vs 25 MA 30.1 vs 27.8	azi vs cefac total AE : NR total GI : 1 vs 1 vomiting and diarrhea : 1 vs 1
Pavlopoulou - 1995	55	clarithromycin vs cefaclor F : 13 vs 11 M : 17 vs 14 MA : 4.01 vs 3.84	clari vs cefac total AE : 3 vs 2 total GI : 1 vs 0 nausea : 1 vs 0
Pestalozza - 1992	30	azithromycin vs amoxicillin/clavulanic F : 5 vs 7 M : 10 vs 8 MA : 2yrs 3mo vs 4yrs 9mo	azi vs amox total AE : NR total GI : NR
Principi - 1995	484	azithromycin vs amoxicillin F : 92 vs 108 M : 150 vs 132 MA : 4.2 vs 4.5	azi vs amox total AE : 11/243 (4.5%) vs 20/240 (8.3%) ? Total GI : 11 vs 24 diarrhea : 6 vs 13 vomiting : 2 vs 7 abd pain 1 vs 3 dyspepsia : 1 vs 1 anorexia : 1 vs 0
Pugliese - 1972	n=?	clindamycin vs erythromycin F : 17 (40%) vs 17 (41%) M : 26 (60%) vs 24 (59%) MA : 7.67 vs 7.22	clinda vs ery total AE : 5 vs 2 total GI : 3 vs 2 diarrhea : 2 vs 1 nausea : 1 vs 0 vomiting : 0 vs 1
Rodriguez - 1996	259	azithromycin vs cefaclor F : 66/125 (52.8%) vs 61/134 (45.5%) M : 59/125 (47.2%) vs 73/134 (54.5%) MA : 4.3 vs 3.6	azi vs cefac total AE : 6 vs 8 total GI : 6 vs 7 diarrhea : 1 (1%) vs 7 (5%) nausea 3 (2%) vs 0 abd pain : 1 (1%) vs 0 eneritis : 1 (1%) vs 0
Rosen - 1983	78	erythromycin vs penicillin F / M : NR MA : NR	ery vs pen total AE : NR total GI : NR diarrhea : 1 vs 0
Rosen - 1984	78	NR	NR

Evidence table 16. Adverse events reported with macrolide use

Study Author Year	Total N enrolled	Mean Age Gender M/F	Side Effects macrolide vs comparator total side effects #/# (%) vs #/# (%) GI side effects #/# (%) vs #/# (%) separate GI type AE if available
Schaad - 1993	389	azithromycin vs co-amoxiclav F : 87/197 vs 71/192 M : 110/197 vs 121/192 MA : 4.5 vs 4.4	azi vs co-amox total AE : 23/197 (11.7%) vs 43/192 (22.4%) total GI : 15/197 vs 36/192 nausea : 0 vs 3 diarrhea : 5 vs 32 abd pain : 7 vs 3 vomiting : 3 vs 5
Trujillo - 1981	40	cefacroxil vs erythromycin F : 10 vs 6 M : 10 vs 14 MA : NR	cefac vs ery total AE : NR total GI : NR
Pharyngitis studies			
Boccazzi, A., 2000	252	ceftibuten vs azithromycin F : 43% vs 46% M : 57% vs 54% MA : 7.9 vs 7.8	azi vs ceftibuten Total SE: 5 pts vs 4 pts GI: 4 pts vs 2
Breese, B.B., 1977	171	amoxicillin vs erythromycin vs Penicillin V F / M : NR MA : NR	erythromycin vs amox vs pcn total SE: 4pts vs 6 pts vs 4 pts total GI : NR vomiting: 1 vs 0 vs 0 pts abd pain: 1 vs 10 pts diarrhea: 2 vs 3 vs 3 pts
Breese, B.B., 1974	339	pen tib vs ery tid vs ery bid vs clinamycin F : NR M : NR MA : NR	pen tib vs (ery tid vs ery bid) vs clina total AE : NR total GI : NR diarrhea/vomiting 0 vs 4 vs 0 diarrhea/cramps 0 vs 0 vs 6
Brook, I., 2001	199	cefprozil vs erythromycin F : 44/87 (51%) vs 42/85 (49%) M : 43/87 (49%) vs 43/85 (51%) MA : 7.5 vs 7.3	erythromycin vs cefprozil drug-related SE: (18/100) 18% vs (11/99) 11% total GI : 19/100 (19%) vs 12/99 (12%) diarrhea: 4% vs 8% vomiting: 6% vs 3% nausea: 5 vs 1% abd pain: 4 vs 0%
Cohen, R., 2002	501	F : 75/169 vs 77/165 vs 80/167 M : 94/169 vs 88/165 vs 87/167 MA : 5.8 vs 6.3 vs 6.0	azithromycin(10) vs azm(20) vs penicillin V total AE : NR abd pain: 33% vs 35% vs 35% vomiting: 21% vs 21% vs 19%
Cremer, J., 1998	122	F : 29/52 vs 29/46 M : 33/52 vs 31/46 MA : 6.0 vs 6.1	azithromycin vs cefaclor (11/62) vs (9/60) diarrhea: (3) vs (6) vomiting: (1) vs (2) abd pain: (7) vs (3)
Derriennic, M., 1993	265	F : 95/265 vs 107/288 M : 170/265 vs 181/288 MA : 27.18 vs 29.12	dirithromycin vs erythromycin total SE: (265) 100% vs (288) 100% diarrhea: (25) 9.4% vs (27) 9.4% abd. pain: (20) 7.5% vs (32) 11.1% nausea: (17) 6.4% vs (28) 9.7% vomiting: (8) 3.0% vs (10) 3.5%
Esposito, S., 1998	637	F : 45/85 vs 42/78 vs 38/82 M : 40/85 vs 36/78 vs 44/82 MA 6.4 vs 5.9 vs 6.8	cefaclor vs amoxicillin vs erythromycin total SE: (6/74) 8.1% vs (10/74) 13.5% vs (8.69)11.6% nausea: (2) vs (1) vs (2) vomiting: (2) vs NR vs (2) diarrhea: (1) vs (6) vs (4) total G.I.: (5) vs (7) vs (8)

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Ginsburg, C.M., 1982	175	F : 41/87 vs 43/88 M : 46/87 vs 45/88 MA : 7.9 vs 8.2	erythromycin estolate vs eryromycin ethylsuccinate SE: NR

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Guthrie, R., 1988 (a) "Erythro…"	189	erythromycin vs amoxicillin F / M : NR MA : NR	total AE : NR total GI : NR
Guthrie, 1988 (b) "Aetiology…"	265	erythromycin ethylsuccinate vs enteric-coated erythromycin F / M : NR MA : NR	ery vs ent ery total AE : 56/131 (43) vs 85/131 (65) total GI : 47/131 (36) vs 74/131 (56)
Hughes, W.T., 1969	381	erythromycin vs erythromycin-sulfas vs sulfamethoxazole F / M : NR MA : NR	ery vs ery-sulf vs sulfa total AE : NR total GI : NR
Kearsley, N.L., 1997	229	F : 58/119 vs 57/110 M : 61/119 vs 53/110 MA : 7.2 vs 6.4	clarythromycin vs amoxicillin n=119 vs n=110 total SE: (9) vs (6) total G.I.: (7) vs (2) nausea: (3) vs NR diarrhea: (3) vs (1) vomiting: (1) vs (1) abd. pain: (1) vs (1)
Lester, R.L., 1974	628	benza vs pen V vs ery vs chloro pal vs 7-chloro 3x vs 7 chloro 4x F / M : NR MA : NR	total AE : NR total GI : NR
Levine, M.K., 1972	107	F : NR M : NR MA : NR	clindamycin vs erythromycin SE: NR
Marchisio, P., 1987	130	F / M : NR MA : NR	erythromycin ethylsuccinate vs josamycin total SE: (12) 17.9% vs (3) 4.8% total GI : 4 vs 0 abd cramp : 3 vs 0 vomiting : 1 vs 0
McCarty, J.M., 1994	1597	study 1: cefprozil vs Penicillin V F : 37/77 (48) vs 35/74 (47) M : 40/77 (52) vs 39/74 (53) MA : 7 vs 8 study 2: cefprozil vs cefaclor F : 347/549 (63) M : 202/549 (37) vs 119/282 (42) MA : 26 vs 26 study 3: cefprozil vs Penicillin V F : 87/183 (48) vs 84/176 (48) M : 96/183 (52) vs 92/176 (82) MA 6 vs 6 study 4: cefprozil vs erythromycin F : 62/128 (48) vs 80/128 (62) M : 66/128 (52) vs 48/128 (38) MA : 7 vs 7	total AE : NR total GI : NR
Melcher, G.P., 1988	61	total F/M : 22 males, 39 females total mean age : 30 F / M : NR MA : NR	total AE : NR total GI : NR
Milatovic, D., 1991	239	F / M : NR MA : NR	cefadroxil vs penicilling vs erythromycin total AE : NR total GI : NR

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Muller, O., 1993		F : 117/193 vs 112/196 M : 76/193 vs 84/196 MA : 30.4 vs 31.3	dirithromycin vs erythromycin n=193 vs n=196 total AE : 28/193 vs 38/196 diarrhea: (9) 4.7% vs (9) 4.6% abd pain: (4) 2.1% vs (7) 3.6% vomiting: (4) 2.1% vs (4) 2.0% nausea: (3) 1.6% vs (13) 6.6%

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Norrby, S.R., 2004	860	F : 171/430 vs 175/428 M : 259/430 vs 175/428 MA : 31.6 vs 31.5	telithromycin vs (penicillin vs clarithromycin) total SE: 224/427 vs 129/424 total GI :119/427 vs 37/424
Quinn, J., 2003	526	F : 148/232 vs 140/231 M : 84/232 vs 91/231 MA : 30.9 vs 30.0	telithromycin vs clarithromycin total SE: (154/229) 67.2% vs (131/228) 57.5% diarrhea: 16.6% vs 7.5% nausea: 10.5% vs 3.9% vomiting: 5.2% vs 0%
Shapera, R.M., 1973	172	pen phen vs pen G vs ery4x vs ery2x F / M : NR MA : NR	total AE : NR total GI : NR
Soebardja, D., 1987	100	spiramycin vs erythromycin F : 21/50 vs 21/47 M : 29/50 vs 26/47 study age range : 6m - 6yrs	spiramycin vs erythromycin total AE : NR total GI : NR
Soekrawinata, T., 1984	100	erythromycin vs spiramycin F : 15/50 vs 19/50 M : 35/50 vs 31/50 MA : NR study age range : 15-50 yrs	erythromycin vs spiramycin total SE: NR total GI : NR nausea: 5 vs - dizziness : 2 vs - dry mouth : 2 vs -
Suprihati, 1984	100	spiramycin vs erythromycin F / M : NR MA : NR	erythromycin vs spiramycin total AE : NR total GI : NR nausea: (7) vs - urticaria: - vs (1)
Syrogiannopoulos, G.A., 2004	626	clari 30 vs clari 15 vs amoxicillin vs penicillin V F : 67/135 vs 64/132 vs 65/135 vs 566/135 M : 68/135 vs 68/132 vs 70/135 vs 69/135 MA : 8 vs 8 vs 7 vs 7	clari 30 vs clari 15 vs amox vs pen total AE : 25/158 vs 21/155 vs 23/155 vs 8/158 total GI : NR
Trujillo, 1981	40	cefadroxil vs erythromycin F : 10 vs 6 M : 10 vs 14 MA : NR	cefad vs ery total AE : NR total GI : NR

Abbreviations used in evidence tables

AB	acute bronchitis
abd	abdominal
ABECB	acute bacterial exacerbation of chronic bronchitis
ABX	antibiotics
amox	amoxicillin
ampi	ampicillin
AOM	acute otitis media
apap	acetaminophen
azi	azithromycin
bid	twice daily
biochem	biochemistry
BP	blood pressure
CB	chronic bronchitis
CBC	complete blood count
CF	cystic fibrosis
CI	contraindication
clari	clarithromycin
clnd	clindamycin
cx	culture
cx	culture
CXR	chest x-ray
D/C	discontinued/discontinuation
d/o	disorder
dir	dirithromycin
dx	diagnosis
EOS	end-of-study
EOT	end-of-therapy
ER	extended-release
erad	eradication
ery	erythromycin
eval	evaluation
exac	exacerbation
exam	examination
f/u	follow-up
FEV	forced expiratory volume
GI	gastrointestinal
GS	Gram stain
H. flu	Haemophilus influenzae
H. paraflu	Haemophilus parainfluenzae
hemat	hematology
hx	history
hypersens	hypersensitivity
infxn	infection
IR	immediate-release
ITT	intention-to-treat
Kleb. pneumo	Klebsiella pneumoniae
Kleb. spp	Klebsiella species
lab	laboratory
LFT	liver function test
M. cat	Moraxella catarrhalis
med	medication
MEF	middle ear fluid
MITT	modified intention-to-treat
mo	month
mod	moderate
N/A	not available
OM	otitis media
P. aeruginosa	Pseudomonas aeruginosa
pcn	penicillin
PE	physical exam
PMH	past medical history
prn	as needed
pt	patient
pt	patient
pulm	pulmonary
qd	once daily
qid	four times a day
resist	resistance/resistant
resp	respiratory
RR	respiratory rate
RTI	respiratory tract infection
S. aureus	Staphylococcus aureus
S. pyog	Streptococcus pyogenes
sig	significant
stat	statistical
strep	streptococcus
suscept	susceptibility
sx	symptom
TB	tuberculosis
temp	temperature
tid	three times a day
TM	tympanic membrane
TMP-SMX	trimethoprim-sulfamethoxazole
TOC	test-of-cure
tx	treatment
URTI	upper respiratory tract infection
VS	vital signs
w/	with
w/d	withdrawal
w/in	within
w/o	without
WBC	white blood cell count
yr	year